CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 76-505

Name: Metronidazole Capsules 375 mg

Sponsor: Able Laboratories, Inc.

Approval Date: November 13, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-505

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-505

APPROVAL LETTER

ANDA 76-505

NOV 13 2003

Able Laboratories, Inc.
Attention: Iva Klemick
6 Hollywood Court, CN 1013
South Plainfield, NJ 07080-4295

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated September 26, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Metronidazole Capsules, 375 mg.

Reference is also made to your amendments dated March 19, March 28, May 12, May 13, and May 20, 2003.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Metronidazole Capsules, 375 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Flagyl® 375 Capsules, of G.D. Searle LLC). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy, which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print.

Submit both copies together with a copy of the final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FDA 2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

11/13/03

cc: ANDA 76-505
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205
HFD-610/Orange Book Staff

Endorsements:
HFD-620/B.Lim/ 10/3/03
HFD-625/S.Liu/ S.H.Liu 10/6/03
HFD-617/W.Pamphile/ 10/3/03
HFD-613/R.Wu/ 10/2/03
HFD-613/J.Grace/ 10/3/2003

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F/T by

APPROVAL

10/14/03

Robert West
10/20/2003
pending resolution of:
1. First-generic CMC audit;
2. DSI inspection status → OAI per Memo dated 9/17/03

Robert West
11/13/2003
O.K. to approve

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-505

APPROVED LABELING

Final Outsert # 10

METRONIDAZOLE CAPSULES
375 mg

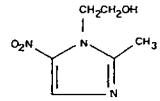
Rx Only

WARNING

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

DESCRIPTION

Metronidazole is an oral synthetic antiprotozoal and antibacterial agent, 2-Methyl-5-nitroimidazole-1-ethanol, which has the following structural formula:



$C_6H_9N_3O_3$ M.W. =171.15

Metronidazole capsules, for oral administration, contains 375 mg of metronidazole USP. Inactive ingredients include: corn starch, and magnesium stearate. In addition, the capsule contains: alcohol, black iron oxide, D&C Red # 33, D&C Yellow # 10, FD&C Blue # 1, FD&C Blue # 2, FD&C Red # 40, gelatin, pharmaceutical glaze, propylene glycol and titanium dioxide.

CLINICAL PHARMACOLOGY

Disposition of metronidazole in the body is similar for both oral and intravenous dosage forms, with an average elimination half-life in healthy humans of 8 hours.

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-(β-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. Renal clearance of metronidazole is approximately 10 mL/min/1.73 m^2.

Metronidazole is the major component appearing in the plasma, with lesser quantities of the 2-hydroxymethyl metabolite also being present. Less than 20% of the circulating metronidazole is bound to plasma proteins. Both the parent compound and the metabolite possess *in vitro* bactericidal activity against most strains of anaerobic bacteria and *in vitro* trichomonacidal activity.

Metronidazole appears in cerebrospinal fluid, saliva, and human milk in concentrations similar to those found in plasma. Bactericidal concentrations of metronidazole have also been detected in pus from hepatic abscesses.

Metronidazole capsules, 375 mg have been shown to have a rate and extent of absorption similar to metronidazole tablets and were bioequivalent at an equal single dose of 750 mg. In a study conducted with 23 adult, healthy, female volunteers, oral administration of two 375-mg metronidazole capsules under fasted conditions produced a mean (± 1 SD) peak plasma concentration (C_{max}) of 21.4 (± 2.8) mcg/mL with a mean T_{max} of 1.6 (± 0.7) hours and a mean area under the plasma concentration-time curve (AUC) of 223 (± 44) mcg•hr/mL. In the same study, three 250-mg metronidazole tablets produced a mean C_{max} of 20.4 (± 3.8) mcg/mL with a mean T_{max} of 1.4 (± 0.4) hours and a mean AUC of 218 (± 50) mcg•hr/mL.

Administration of metronidazole capsules, 375 mg with food does not affect the extent of absorption of metronidazole; however, the presence of food results in a lower C_{max} and a delayed T_{max} compared to fasted conditions. In a study of 14 healthy, adult, female volunteers, administration of metronidazole capsules, 375 mg under fasting conditions produced a mean C_{max} of 10.9 (± 1.5) mcg/mL, a mean T_{max} of 1.5 (± 1.4) hours, and a mean AUC of 110 (± 34) mcg•hr/mL compared to a mean C_{max} of 8.6 (± 1.6) mcg/mL, a mean T_{max} of 4.2 (± 1.7) hours, and a mean AUC of 99 (± 14) mcg•hr/mL under fed conditions.

Decreased renal function does not alter the single-dose pharmacokinetics of metronidazole. However, plasma clearance of metronidazole is decreased in patients with decreased liver function.

Microbiology:

Metronidazole exerts antimicrobial effects in an anaerobic environment by the following possible mechanism: Once metronidazole enters the organism, the drug is reduced by intracellular electron transport proteins. Because of this alteration to the metronidazole molecule, a concentration gradient is maintained which promotes the drug's intracellular transport. Presumably, free radicals are formed which, in turn, react with cellular components resulting in death of the microorganism.

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

Gram-positive anaerobes:
Clostridium species
Eubacterium species
Peptococcus niger
Peptostreptococcus species

Gram-negative anaerobes:
Bacteroides fragilis group (*B. fragilis, B. distasonis, B. ovatus, B. thetaiotaomicron, B. vulgatus*)
Fusobacterium species

Protozoal parasites:
Entamoeba histolytica
Trichomonas vaginalis

The following *in vitro* data are available, **but their clinical significance is unknown:**
Metronidazole exhibits *in vitro* minimal inhibitory concentrations (MIC's) of 8 mcg/mL or less against most (≥ 90%) strains of the following microorganisms; however, the safety and effectiveness of metronidazole in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Gram-negative anaerobes:
Bacteroides fragilis group (*B. caccae, B. uniformis*)
Prevotella species (*P. bivia, P. buccae, P. disiens*)

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

Susceptibility Tests:
Dilution techniques:

Quantitative methods that are used to determine minimum inhibitory concentrations provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. For anaerobic bacteria, the susceptibility to metronidazole can be determined by the reference agar dilution method or by alternate standardized test methods[1]. The MIC values obtained should be interpreted according to the following criteria:

MIC (mcg/mL)	Interpretation
≤ 8	Susceptible (S)
16	Intermediate (I)
≥ 32	Resistant (R)

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

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by usually achievable concentrations of the antimicrobial compound in the blood. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that usually achievable concentrations of the antimicrobial compound in the blood are unlikely to be inhibitory and other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. Standard metronidazole powder should provide the following MIC values:

Microorganism	MIC (mcg/mL)
Bacteroides fragilis ATCC 25285	0.25-1.0
Bacteroides thetaiotaomicron ATCC 29741	0.5-2.0

INDICATIONS AND USAGE

Symptomatic Trichomoniasis. Metronidazole capsules, 375 mg are indicated for the treatment of symptomatic trichomoniasis in females and males when the presence of the trichomonad has been confirmed by appropriate laboratory procedures (wet smears and/or cultures).

Asymptomatic Trichomoniasis. Metronidazole capsules, 375 mg are indicated in the treatment of asymptomatic females when the organism is associated with endocervicitis, cervicitis, or cervical erosion. Since there is evidence that presence of the trichomonad can interfere with accurate assessment of abnormal cytological smears, additional smears should be performed after eradication of the parasite.

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

Amebiasis. Metronidazole capsules, 375 mg are indicated in the treatment of acute intestinal amebiasis (amebic dysentery) and amebic liver abscess.

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

Anaerobic Bacterial Infections. Metronidazole capsules, 375 mg are indicated in the treatment of serious infections caused by susceptible anaerobic bacteria. Indicated surgical procedures should be performed in conjunction with metronidazole therapy. In a mixed aerobic and anaerobic infection, antimicrobials appropriate for the treatment of the aerobic infection should be used in addition to metronidazole capsules, 375 mg.

In the treatment of most serious anaerobic infections, intravenous metronidazole is usually administered initially. This may be followed by oral therapy with metronidazole capsule, 375 mg at the discretion of the physician.

INTRA-ABDOMINAL INFECTIONS, including peritonitis, intra-abdominal abscess, and liver abscess, caused by *Bacteroides* species including the *B. fragilis* group (*B. fragilis, B. distasonis, B. ovatus, B. thetaiotaomicron, B. vulgatus*), *Clostridium* species, *Eubacterium* species, *Peptococcus niger,* or *Peptostreptococcus* species.

SKIN AND SKIN STRUCTURE INFECTIONS caused by *Bacteroides* species including the *B. fragilis* group, *Clostridium* species, *Peptococcus niger, Peptostreptococcus* species, or *Fusobacterium* species.

GYNECOLOGIC INFECTIONS, including endometritis, endomyometritis, tubo-ovarian abscess, and postsurgical vaginal cuff infection, caused by *Bacteroides* species including the *B. fragilis* group, *Clostridium* species, *Peptococcus niger,* or *Peptostreptococcus* species.

BACTERIAL SEPTICEMIA caused by *Bacteroides* species including the *B. fragilis* group or *Clostridium* species.

BONE AND JOINT INFECTIONS (as adjunctive therapy) caused by *Bacteroides* species including the *B. fragilis* group.

CENTRAL NERVOUS SYSTEM (CNS) INFECTIONS, including meningitis and brain abscess, caused by *Bacteroides* species including the *B. fragilis* group.

LOWER RESPIRATORY TRACT INFECTIONS, including pneumonia, empyema, and lung abscess, caused by *Bacteroides* species including the *B. fragilis* group.

ENDOCARDITIS caused by *Bacteroides* species including the *B. fragilis* group.

CONTRAINDICATIONS

Metronidazole capsules, 375 mg are contraindicated in patients with a prior history of hypersensitivity to metronidazole or other nitroimidazole derivatives.

In patients with trichomoniasis, metronidazole capsules, 375 mg are contraindicated during the first trimester of pregnancy (see **PRECAUTIONS**).

WARNINGS

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

PRECAUTIONS

General: Patients with severe hepatic disease metabolize metronidazole slowly, with resultant accumulation of metronidazole and its metabolites in the plasma. Accordingly, for such patients, doses below those usually recommended should be administered cautiously. Known or previously unrecognized candidiasis may present more prominent symptoms during therapy with metronidazole and requires treatment with a candidacidal agent.

Information for Patients: Alcoholic beverages should be avoided while taking metronidazole capsules, 375 mg and for at least three days afterward (see **Drug Interactions**).

Laboratory Tests: Metronidazole is a nitroimidazole and should be used with caution in patients with evidence of or history of blood dyscrasia. A mild leukopenia has been observed during its administration; however, no persistent hematologic abnormalities attributable to metronidazole have been

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observed in clinical studies. Total and differential leukocyte counts are recommended before and after therapy for trichomoniasis and amebiasis, especially if a second course of therapy is necessary, and before and after therapy for anaerobic infections.

Drug Interactions: Metronidazole has been reported to potentiate the anticoagulant effect of warfarin and other oral coumarin anticoagulants, resulting in a prolongation of prothrombin time. This possible drug interaction should be considered when metronidazole is prescribed for patients on this type of anticoagulant therapy.

The simultaneous administration of drugs that induce microsomal liver enzymes, such as phenytoin or phenobarbital, may accelerate the elimination of metronidazole, resulting in reduced plasma levels; impaired clearance of phenytoin has also been reported.

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. 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.

Alcoholic beverages should not be consumed during metronidazole therapy and for at least three days afterward because abdominal cramps, nausea, vomiting, headaches and flushing may occur.

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.

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 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 ($NAD^+ \rightleftarrows NADH$). 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: Metronidazole has shown evidence of carcinogenic activity in a number of studies involving chronic, oral administration in mice and rats, but similar studies in the hamster gave negative results.

Prominent among the effects in the mouse was the promotion of pulmonary tumorigenesis. This has been observed in all six reported studies in that species, including one study in which the animals were dosed on an intermittent schedule (administration during every fourth week only). At very high dose levels (approximately 1500 mg/m² which is approximately 3 times the most frequently recommended dose for a 50 kg adult based on mg/m²) there was a statistically significant increase in the incidence of malignant liver tumors in males. Also, the published results of one of the mouse studies indicate an increase in the incidence of malignant lymphomas as well as pulmonary neoplasms associated with lifetime feeding of the drug. All these effects are statistically significant.

Several long-term, oral-dosing studies in the rat have been completed. There were statistically significant increases in the incidence of various neoplasms, particularly in mammary and hepatic tumors, among female rats administered metronidazole over those noted in the concurrent female control groups.

Two lifetime tumorigenicity studies in hamsters have been performed and reported to be negative.

Metronidazole has shown mutagenic activity in a number of *in vitro* assay systems. *In vivo* studies have failed to demonstrate a potential for genetic damage.

Fertility studies have been performed in mice at doses up to six times the maximum recommended human dose based on mg/m² and have revealed no evidence of impaired fertility.

Pregnancy:
Teratogenic Effects: Pregnancy Category B. Metronidazole crosses the placental barrier and enters the fetal circulation rapidly. Reproduction studies have been performed in rats at doses up to five times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to metronidazole. No fetotoxicity was observed when metronidazole was administered orally to pregnant mice at 60 mg/m²/day, which is approximately 10% of the human dose when expressed as mg/m². However, in a single small study where the drug was administered intraperitoneally, some intrauterine deaths were observed. The relationship of these findings to the drug is unknown. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, and because metronidazole is a carcinogen in rodents, this drug should be used during pregnancy only if clearly needed (see **CONTRAINDICATIONS**).

Metronidazole use in the second and third trimesters of pregnancy should be restricted to those patients in whom alternative treatment has been inadequate. Use of metronidazole in the first trimester should be carefully evaluated because metronidazole crosses the placental barrier and its effects on human fetal organogenesis are not known (see above).

Nursing Mothers: Because of the potential for tumorigenicity shown for metronidazole in mouse and rat studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Metronidazole is secreted in human milk in concentrations similar to those found in plasma.

Geriatric Use: No overall differences have been reported in safety and effectiveness between younger and older individuals, but greater sensitivity of some older individuals cannot be ruled out. Systemic exposure to the active metabolite, 2-hydroxymethyl metronidazole, is higher in the elderly.

Metronidazole is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Although decreased renal function does not alter the single dose pharmacokinetics of metronidazole, because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Plasma clearance of metronidazole is decreased in patients with decreased liver function. Therefore, in elderly patients, monitoring of serum levels may be necessary to adjust the metronidazole dose accordingly.

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

ADVERSE REACTIONS
The following reactions have also been reported during treatment with metronidazole.

Central Nervous System: Two serious adverse reactions reported in patients treated with metronidazole have been convulsive seizures 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 dizziness, vertigo, incoordination, ataxia, confusion, irritability, depression, weakness and insomnia (see **WARNINGS**).

Gastrointestinal: The most common adverse reactions reported have been referable to the gastrointestinal tract, particularly nausea reported by about 12% of patients, sometimes accompanied by headache, anorexia, and occasionally vomiting; diarrhea; epigastric distress; and abdominal cramping. Constipation has also been reported.

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. Rare cases of pancreatitis, which generally abated on withdrawal of the drug, have been reported.

Hematopoietic: Reversible neutropenia (leukopenia); rarely, reversible thrombocytopenia.
Cardiovascular: Flattening of the T-wave may be seen in electrocardiographic tracings.
Hypersensitivity: Urticaria, erythematous rash, flushing, nasal congestion, dryness of the mouth (or vagina or vulva), and fever.

Renal: Dysuria, cystitis, polyuria, incontinence, and a sense of pelvic pressure. Instances of darkened urine have been reported by approximately one patient in 100,000. Although the pigment which is probably responsible for this phenomenon has not been positively identified, it is almost certainly a metabolite of metronidazole and seems to have no clinical significance.

Other: Proliferation of *Candida* in the vagina, dyspareunia, decrease of libido, proctitis, and fleeting joint pains sometimes resembling "serum sickness." If patients receiving metronidazole drink alcoholic beverages, they may experience abdominal distress, nausea, vomiting, flushing, or headache. A modification of the taste of alcoholic beverages has also been reported.

Patients with Crohn's disease are known to have an increased incidence of gastrointestinal and certain extraintestinal cancers. There have been some reports in the medical literature of breast and colon cancer in Crohn's disease patients who have been treated with metronidazole at high doses for extended periods of time. A cause and effect relationship has not been established. Crohn's disease is not an approved indication for metronidazole capsules, 375 mg.

OVERDOSAGE
Single oral doses of metronidazole, up to 15 g, have been reported in suicide attempts and accidental overdoses. Symptoms reported include nausea, vomiting, and ataxia.

Oral metronidazole has been studied as a radiation sensitizer in the treatment of malignant tumors. Neurotoxic effects, including seizures and peripheral neuropathy, have been reported after 5 to 7 days of doses of 6 to 10.4 g every other day.

Treatment: There is no specific antidote for metronidazole overdose; therefore, management of the patient should consist of symptomatic and supportive therapy.

DOSAGE AND ADMINISTRATION
In elderly patients, the pharmacokinetics of metronidazole may be altered, and, therefore, monitoring of serum levels may be necessary to adjust the metronidazole dosage accordingly.

Trichomoniasis:
In the Female:
Seven-day course of treatment — 375 mg two times daily for seven consecutive days.

A seven-day course of treatment may minimize reinfection by protecting the patient long enough for the sexual contacts to obtain treatment. Pregnant patients should not be treated during the first trimester (see **CONTRAINDICATIONS** and **PRECAUTIONS**).

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

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

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

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

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

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

The usual adult oral dosage is 7.5 mg/kg every 6 hours. A maximum of 4 g should not be exceeded during a 24-hour period.

The usual duration of therapy is 7 to 10 days; however, infections of the bone and joint, lower respiratory tract, and endocardium may require longer treatment.

Patients with severe hepatic disease metabolize metronidazole slowly, with resultant accumulation of metronidazole and its metabolites in the plasma. Accordingly, for such patients, doses below those usually recommended should be administered cautiously. Close monitoring of plasma metronidazole levels[2] and toxicity is recommended.

The dose of metronidazole should not be specifically reduced in anuric patients because accumulated metabolites may be rapidly removed by dialysis.

HOW SUPPLIED
Metronidazole capsules, 375 mg are supplied as: 375 mg capsules, off white to light yellow powder filled in #1 capsules, opaque yellow cap imprinted "A" and opaque grey body imprinted "353" in black ink and are available as the following:

Bottles of 30
Bottles of 50
Bottles of 100
Bottles of 500
Bottles of 1000

Store at controlled room temperature 15° - 30°C (59° - 86°F). [See USP].

Protect from light.

Dispense in a tight, well-closed, light-resistant container as defined in the USP, with a child-resistant closure (as required).

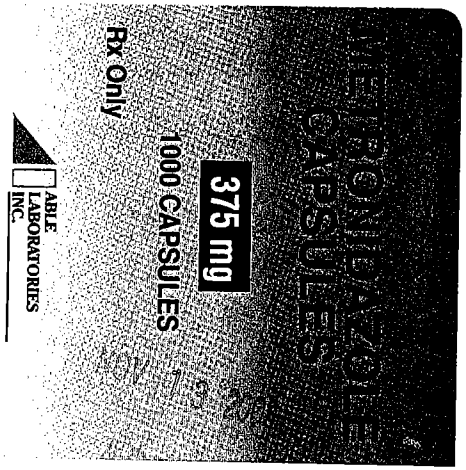
REFERENCES

1. National Committee for Clinical Laboratory Standards, Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria — Third Edition. Approved Standard NCCLS Document M11-A3, Vol. 13, No. 26, NCCLS, Villanova, PA, December, 1993.

2. Ralph ED, Kirby WMM. Bioassay of metronidazole with either anaerobic or aerobic incubation. *J. Infect. Dis.* 1975; 132(Nov): 587-591 or Gulaid et al. Determination of metronidazole and its major metabolites in biological fluids by high pressure liquid chromatography. *Br. J. Clin. Pharmacol.* 1978; 6:430-432.

Manufactured by:
ABLE LABORATORIES, INC.
6 Hollywood Court, CN 1013
South Plainfield, NJ 07080-4295

Manufacturer's Code 53265
IN16062/02 VC8177 05/03



EACH CAPSULE CONTAINS:
Metronidazole, USP.....375 mg

USUAL ADULT DOSAGE: See package outsert for complete dosage recommendations.

DISPENSE in a tight, well-closed, light-resistant container as defined in the USP, with a child-resistant closure (as required).

STORE at controlled room temperature between 15° - 30°C (59° - 86°F). [See USP].

Protect from light.

Mfg. by: ABLE LABORATORIES, INC.
SOUTH PLAINFIELD, NJ 07080

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03/03

Manufacturer's Code
53265

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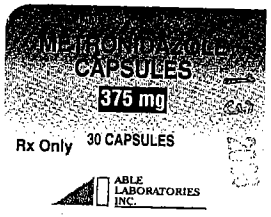
LOT NO.:

EXP. DATE:



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Mfg. by: ABLE LABORATORIES, INC.
SOUTH PLAINFIELD, NJ 07080

LB10279/01
03/03

Manufacturer's Code
53265

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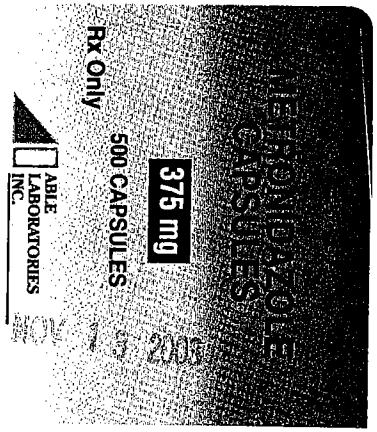
LOT NO.:

EXP. DATE:



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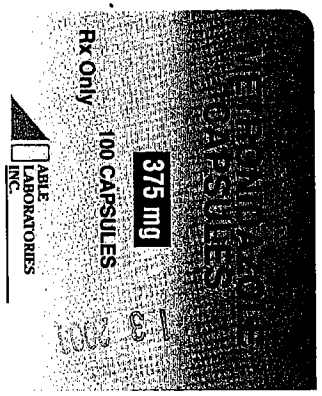
LB10281/01
03/03

Manufacturer's Code
53265

N 3 53265-353-50 4

LOT NO.:

EXP. DATE:



EACH CAPSULE CONTAINS:
Metronidazole, USP.....375 mg

USUAL ADULT DOSAGE: See package outsert for complete dosage recommendations.

DISPENSE in a tight, well-closed, light-resistant container as defined in the USP, with a child-resistant closure (as required).

STORE at controlled room temperature between 15° - 30°C (59° - 86°F). [See USP].

Protect from light.

Mfg. by: ABLE LABORATORIES, INC.
SOUTH PLAINFIELD, NJ 07080

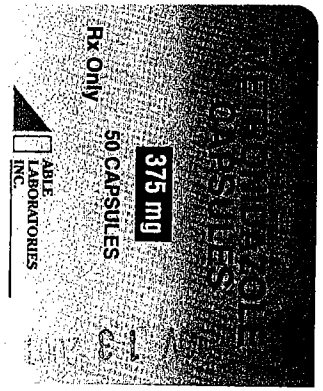
LB10280/01
03/03

Manufacturer's Code
53265

N 3 53265-353-10 8

LOT NO.:

EXP. DATE:



EACH CAPSULE CONTAINS:
Metronidazole, USP.....375 mg

USUAL ADULT DOSAGE: See package outsert for complete dosage recommendations.

DISPENSE in a tight, well-closed, light-resistant container as defined in the USP, with a child-resistant closure (as required).

STORE at controlled room temperature between 15° - 30°C (59° - 86°F). [See USP].

Protect from light.

Mfg. by: ABLE LABORATORIES, INC.
SOUTH PLAINFIELD, NJ 07080

LB10279/01
03/03

Manufacturer's Code
53265

N 3 53265-353-05 4

LOT NO.:

EXP. DATE:

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-505

LABELING REVIEW(S)

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76,505

Date of Submission: September 26, 2002 (Original Submission)

Applicant's Name: Able Laboratories, Inc.

Established Name: Metronidazole Capsules, 375 mg

Labeling Deficiencies:

1. CONTAINER (Bottles of 30, 50, 100, 500 and 1000)
   We encourage you to add "Protect from light." to the storage statement.

2. INSERT
   a. DESCRIPTION- "Metronidazole capsules, for oral administration, contains..." [insert comma]
   b. CLINICAL PHARMACOLOGY, sixth paragraph, second sentence- "...C_{max} of 8.6 (±1.6)..."
   c. PRECAUTIONS, Drug Interactions, second paragraph- "...phenytoin has also been reported."
   d. HOW SUPPLIED-refer to comment 1.

Please revise your labels and labeling, as instructed above, and submit 12 copies of final printed labels and labeling.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 24		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)			
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			x
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X

Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		X	

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD: **FIRST GENERIC**

1. MODEL LABELING - This review is based on the labeling of Flagyl® Capsules by Searle (NDA #020334, revised 2/25/95; approved May 3, 1995; AR 9/27/95). NDA 20-334/S-001 that provides for the addition of a "Geriatric Use" subsection is pending as of March 3, 2003.

   Drug substance is USP and Drug product is non-USP.

2. PATENTS AND EXCLUSIVITIES

Patent Data For NDA 20-334

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	None	None	There are no unexpired patents for this product in the Orange Book Database.	N/A	None

Exclusivity Data For NDA 20-334

Code/sup	Expiration	Use Code	Description	How Filed	Labeling Impact
			There are no unexpired exclusivities	N/A	None

The firm's statements are accurate. [Vol. B1.1, Pg. 21 & 26]

3. MANUFACTURING FACILITY (Vol. B1.2, pg. 3539)
   Able Laboratories, Inc.,
   6 Hollywood Court
   CN 1013
   South Plainfield, NJ 07080-4295

4. STORAGE CONDITIONS:
   NDA - Store at controlled room temperature 15°C-30°C (59° F-86°F)
   ANDA - Store at controlled room temperature [redacted] 15°C and 30°C (59° F and 86°F)(see USP)
   The RLD insert storage statement for the 250 mg and 500 mg has "Protect from light." I will encourage the firm to add this statement to their container and insert label and labeling.
5. DISPENSING RECOMMENDATIONS:
   NDA - Pharmacist: Dispense in a well closed container with a child-resistant closure
   ANDA - Pharmacist: Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

7. PRODUCT LINE:
   The innovator markets its product in bottles of 50 and 100 capsules and Carton of 100 unit dose.
   The applicant proposes to market its product in HDPE bottles of 30, 50, 100, 500 and 1000 capsules.

8. CONTAINER/CLOSURE SYSTEM: (Vol. B1.3, pg. 3778)

Size	Packaging configuration
30 Capsules	45 cc HDPE white bottle, 33 mm ribbed plastic cap, **CRC**, ——— liner.
50 Capsules	120 cc HDPE white bottle, 38 mm ribbed smooth plastic cap, **CRC**, ——— liner (———).
100 Capsules	120 cc HDPE white bottle, 38 mm ribbed smooth plastic cap, ——— liner.
500 Capsules	625 cc HDPE white bottle, 53 mm ribbed smooth plastic cap, ——— liner.
1000 Capsules	1250 cc HDPE white bottle, 70 mm ribbed smooth plastic cap, ——— liner.

9. PRODUCT DESCRIPTION:

The capsule debossing(s) have been accurately described in the HOW SUPPLIED section as required by 21 CFR
206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). The tablets are described as follows:

off white to light yellow powder filled in #1 capsules, opaque yellow cap imprinted "A" and opaque grey body imprinted "353" in black ink [Vol. B1.3, pg. 3964]

10. INACTIVE INGREDIENTS:
The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 3394.B1.2]

11. BIOEQUIVALENCE: pending as of February 21, 2003

Date of Review: March 3, 2003 Date of Submission: September 26, 2002 (Original Submission)

Primary Reviewer: Ruby Wu Date: 3/5/03

Team Leader: John Grace Date: 3/6/2003

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cc: ANDA 76-505
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Review

APPEARS THIS WAY
ON ORIGINAL

4 1

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:	76-505
Date of Submission:	March 28, 2003 (FPL)
Applicant's Name:	Able Laboratories, Inc.
Established Name:	Metronidazole Capsules, 375 mg

Labeling Deficiencies:

1. CONTAINER (Bottles of 30, 50, 100, 500 and 1000)
   Satisfactory in final print.

2. INSERT
   A. TITLE, Warning, second sentence: "...reserved for the conditions..."
   B. CLINICAL PHARMACOLOGY
      i. Fifth paragraph, last sentence: "...(± 0.4)..." [insert space after "±"]
      ii. Protozoal parasites, second paragraph: "...(≥ 90%)..." [insert space after "≥"]
   C. PRECAUTIONS, Geriatric Use- Due to changes in the insert labeling for the reference listed drug, (Flagyl® Capsules by Searle NDA 20-334/S-001; revised 5/5/99; approved 4/23/03), please revise the Geriatric Use subsection to read as follows:
   "No overall differences have been reported in safety and effectiveness between younger and older individuals, but greater sensitivity of some older individuals cannot be ruled out. Systemic exposure to the active metabolite, 2-hydroxymethyl metronidazole, is higher in the elderly.
   Metronidazole is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Although decreased renal function does not alter the single dose pharmacokinetics of metronidazole, because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it maybe useful to monitor renal function.
   Plasma clearance of metronidazole is decreased in patients with decreased liver function. Therefore, in elderly patients, monitoring of serum levels may be necessary to adjust the metronidazole dose accordingly."
   D. REFERENCES, number 2: "...132(Nov): 587-591..." [insert space after "132(Nov):"]

Please revise your labels and labeling, as instructed above, and submit 12 copies of final printed labels and labeling.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachment: Innovator's insert labeling

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: (Bottles of 30, 50, 100, 500 and 1000)
Satisfactory in final print as of the March 28, 2003 submission (Vol. B. 2.1)

Insert Labeling:
Satisfactory in final print as of the March 28, 2003 (Vol. B. 2.1, Rev. 03/03)

Revisions needed post-approval: YES. The following are requested insert labeling revisions from my review of your amendment dated March 28, 2003 for ANDA 76-505 for Metronidazole Capsules, 375 mg. The revisions are **"POST-APPROVAL"** revisions and may be submitted in an annual report, provided the changes are described in full.

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Flagyl® Capsules
NDA Number: 20-334
NDA Drug Name: Flagyl® Capsules
NDA Firm: Searle
Date of Approval of NDA Insert and supplement: NDA #020334/S-001, revised 5/5/99; approved 4/23/03
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: Side-by-side comparison with innovator labels in jacket.

PATENTS/EXCLUSIVITIES

Patent Data: NDA 20-334

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	***None***	None	There are no unexpired patents for this product in the Orange Book Database.	N/A	None

Exclusivity Data: NDA 20-334

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	*N/A*	*None*

APPEARS THIS WAY
ON ORIGINAL

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 24		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)			
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			x
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	

Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		X	

NOTES/QUESTIONS TO THE CHEMIST:

/

FOR THE RECORD: **FIRST GENERIC**

1. MODEL LABELING - This review is based on the labeling of Flagyl® Capsules by Searle (NDA #020334/S-001, revised 5/5/99; approved 4/23/03).

   Drug substance is USP and Drug product is non-USP.

2. PATENTS AND EXCLUSIVITIES

Patent Data For NDA 20-334

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	None	None	There are no unexpired patents for this product in the Orange Book Database.	N/A	None

Exclusivity Data For NDA 20-334

Code/sup	Expiration	Use Code	Description	How Filed	Labeling Impact
			There are no unexpired exclusivities	N/A	None

The firm's statements are accurate. [Vol. B1.1, Pg. 21 & 26]

3. MANUFACTURING FACILITY (Vol. B1.2, pg. 3539)
   Able Laboratories, Inc.,
   6 Hollywood Court
   CN 1013
   South Plainfield, NJ 07080-4295

4. STORAGE CONDITIONS:
   NDA - Store at controlled room temperature 15°C-30°C (59° F-86°F)
   ANDA - Store at controlled room temperature. ——— 15°C and 30°C (59° F and 86°F)(see USP) . Protect from light.
   Per chemist Bing Cai's email dated 3/26/03, this product may be considered as "light sensitive"

5. DISPENSING RECOMMENDATIONS:
   NDA - Pharmacist: Dispense in a well closed container with a child-resistant closure
   ANDA - Pharmacist: Dispense in a tight, well-closed, light-resistant container as defined in the USP, with a child-resistant closure (as required).

7. PRODUCT LINE:
   The innovator markets its product in bottles of 50 and Carton of 100 unit dose.
   The applicant proposes to market its product in HDPE bottles of 30, 50, 100, 500 and 1000 capsules.

8. CONTAINER/CLOSURE SYSTEM: (Vol. B1.3, pg. 3778)

Size	Packaging configuration
30 Capsules	45 cc HDPE white bottle, 33 mm ribbed plastic cap, **CRC**, ——— liner.
50 Capsules	120 cc HDPE white bottle, 38 mm ribbed smooth plastic cap, **CRC**, ——— liner (———).

100 Capsules	120 cc HDPE white bottle, 38 mm ribbed smooth plastic cap, —— liner.
500 Capsules	625 cc HDPE white bottle, 53 mm ribbed smooth plastic cap, —— liner.
1000 Capsules	1250 cc HDPE white bottle, 70 mm ribbed smooth plastic cap, —— liner.

9. PRODUCT DESCRIPTION:

The capsule debossing(s) have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). The capsules are described as follows:

off white to light yellow powder filled in #1 capsules, opaque yellow cap imprinted "A" and opaque grey body imprinted "353" in black ink [Vol. B1.3, pg. 3964]

10. INACTIVE INGREDIENTS:
The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 3394.B1.2]

11. BIOEQUIVALENCE: pending as of April 28, 2003.

Date of Review: April 28, 2003 Date of Submission: March 28, 2003

Primary Reviewer: Ruby Wu Date: 4/30/03

Team Leader: John Grace Date: 4/29/2003

cc: ANDA 76-505
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Review

APPEARS THIS WAY
ON ORIGINAL

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-505
Date of Submission: May 20, 2003 (Amendment-FPL)
Applicant's Name: Able Laboratories, Inc.
Established Name: Metronidazole Capsules, 375 mg

APPROVAL SUMMARY:

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: (Bottles of 30, 50, 100, 500 and 1000)
Satisfactory in final print as of the March 28, 2003 submission (Vol. A. 2.1; Exhibits ~~4-8~~ 3-7)

Insert Labeling:
Satisfactory in final print as of the May 20, 2003 (Vol. A. 2.1, Rev. 05/03; Exhibit 3)

Revision needed post-approval: YES. The following is a requested insert labeling revision from my review of your amendment dated May 20, 2003 for ANDA 76-505 for Metronidazole Capsules, 375 mg. The revision is a **"POST-APPROVAL"** revision and may be submitted in an annual report provided the change is described in full.

Carcinogeneisis, Mutagenesis, Impariment of Fertility, second paragraph, third sentence: "...most frequently recommended human dose...."

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Flagyl® Capsules
NDA Number: 20-334
NDA Drug Name: Flagyl® Capsules
NDA Firm: Searle
Date of Approval of NDA Insert and supplement: NDA #020334/S-001, revised 5/5/99; approved 4/23/03
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: Side-by-side comparison with innovator labels in jacket.

PATENTS/EXCLUSIVITIES

Patent Data: NDA 20-334

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	***None***	None	There are no unexpired patents for this product in the Orange Book Database.	N/A	None

Exclusivity Data: NDA 20-334

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	*N/A*	*None*

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N/A
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 24		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)			
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			x
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	

Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		X	

NOTES/QUESTIONS TO THE CHEMIST:

/

FOR THE RECORD: **FIRST GENERIC**

1. MODEL LABELING - This review is based on the labeling of Flagyl® Capsules by Searle (NDA #020334/S-001, revised 5/5/99; approved 4/23/03).

   Drug substance is USP and Drug product is non-USP.

2. PATENTS AND EXCLUSIVITIES

Patent Data For NDA 20-334

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	None	None	There are no unexpired patents for this product in the Orange Book Database.	N/A	None

Exclusivity Data For NDA 20-334

Code/sup	Expiration	Use Code	Description	How Filed	Labeling Impact
			There are no unexpired exclusivities	N/A	None

The firm's statements are accurate. [Vol. B1.1, Pg. 21 & 26]

3. MANUFACTURING FACILITY (Vol. B1.2, pg. 3539)
   Able Laboratories, Inc.,
   6 Hollywood Court
   CN 1013
   South Plainfield, NJ 07080-4295

4. STORAGE CONDITIONS:
   NDA - Store at controlled room temperature 15°C-30°C (59° F-86°F)
   ANDA - Store at controlled room temperature ——— 15°C and 30°C (59° F and 86°F)(see USP) . Protect from light.
   Will ask firm to revise storage statement to read: " Store at 20°-25°C (68°-77°F) excursions permitted to 15°-30°C (59°-86°F)[see USP Controlled Room Temperature]" per Richard Adams email.
   Per chemist Bing Cai's email dated 3/26/03, this product may be considered as "light sensitive"

5. DISPENSING RECOMMENDATIONS:
   NDA - Pharmacist: Dispense in a well closed container with a child-resistant closure
   ANDA - Pharmacist: Dispense in a tight, well-closed, light-resistant container as defined in the USP, with a child-resistant closure (as required).

7. PRODUCT LINE:
   The innovator markets its product in bottles of 50 and Carton of 100 unit dose.
   The applicant proposes to market its product in HDPE bottles of 30, 50, 100, 500 and 1000 capsules.

8. CONTAINER/CLOSURE SYSTEM: (Vol. B1.3, pg. 3778)

Size	Packaging configuration
30 Capsules	45 cc HDPE white bottle, 33 mm ribbed plastic cap, **CRC**, ——— liner.

50 Capsules	120 cc HDPE white bottle, 38 mm ribbed smooth plastic cap, **CRC**, —— liner ——
100 Capsules	120 cc HDPE white bottle, 38 mm ribbed smooth plastic cap, —— liner.
500 Capsules	625 cc HDPE white bottle, 53 mm ribbed smooth plastic cap, —— liner.
1000 Capsules	1250 cc HDPE white bottle, 70 mm ribbed smooth plastic cap, —— liner.

9. PRODUCT DESCRIPTION:

The capsule debossing(s) have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). The capsules are described as follows:

off white to light yellow powder filled in #1 capsules, opaque yellow cap imprinted "A" and opaque grey body imprinted "353" in black ink [Vol. B1.3, pg. 3964]

10. INACTIVE INGREDIENTS:
The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 3394.B1.2]

11. BIOEQUIVALENCE: pending as of June 11, 2003.

Date of Review: June 11, 2003 Date of Submission: May 20, 2003

Primary Reviewer: Ruby Wu RWu Date: 6/11/03

Team Leader: John Grace John M Grace Date: 6/12/2003

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cc: ANDA 76-505
DUP/DIVISION FILE
HFD-613/RWu/JGrace (no cc)
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Review

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-505

CHEMISTRY REVIEW(S)

ANDA 76-505

Metronidazole Capsules, 375 mg

Able Laboratories, Inc.

Benjamin Lim, Ph.D.
Division of Chemistry I

Table of Contents

APPEARS THIS WAY
ON ORIGINAL

Chemistry Review Data Sheet

1. ANDA 76-505

2. REVIEW #: 1

3. REVIEW DATE: November 18, 2002

4. REVIEWER: Benjamin Lim, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
FDA (DBE) letter	December 11, 2001
Original Submission	September 26, 2002 (Acceptable for filing September 27, 2002)
FDA Acknowledgment letter	October 30, 2002

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	September 26, 2002
Gratuitous Amendment (container/closure testing)	November 19, 2002
Gratuitous Amendment (editorial correction)	December 20, 2002

7. NAME & ADDRESS OF APPLICANT:

Name:	Able Laboratories, Inc.
Address:	6 Hollywood Court, CN1013 South Plainfield, NJ 07080-4295
Representative:	Shashikant Shah, R.Ph.
Telephone:	(908) 754-2253

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Metronidazole Capsules

9. LEGAL BASIS FOR SUBMISSION:

a) The basis for Able Laboratories, Inc.'s proposed ANDA for Metronidazole Capsules, 375 mg is the approved, reference listed drug Flagyl 375 (metronidazole capsules, 375 mg), the subject of NDA #020334, approved May 3, 1995, held by GD Searle LLC.

b) According to the information published in Electronic Orange Book, Approved Drug Products with Therapeutic Equivalence Evaluations, there is no patent or exclusivity listed for this drug product.

10. PHARMACOL. CATEGORY: Antibacterial Agents

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 375 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

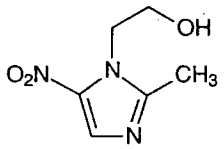
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Metronidazole. *1H*-Imidazole-1-ethanol, 2-methyl-5-nitro-. $C_6H_9N_3O_3$. 171.16. 443-48-1.



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
—	II	—	—	3	A	10/8/2002	Reviewed by K. Woodland
13 DMFs	III	See Item 26	—	4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending		
Methods Validation	N/A		
Labeling	Pending		
Bioequivalence	Pending		
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 76-505

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not approvable due to minor deficiencies

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not applicable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Able's proposed drug product, Metronidazole Capsules, 375 mg, is based on the listed reference drug, FLAGYL 375 (metronidazole capsules, 375 mg), of G.D. Searle LLC (NDA #20-334). Able's drug product is off white to light yellow powder filled in #1 capsules, opaque yellow cap imprinted "A" and opaque grey body imprinted "353" in black ink. Able's Metronidazole Capsules, 375 mg is packaged in HDPE bottles of 30, 50, 100, 500 and 1000 capsules.

Metronidazole, USP drug substance is a white to pale yellow crystals or crystalline powder. The drug substance used by Able is manufactured by [redacted] and the DMF #[redacted] referenced for the drug substance was found adequate on 10/08/2002.

Metronidazole Capsules, 375 mg is not an USP compendial item but the proposed [redacted] assay methods are exactly same as methods provided in the Able's ANDA 76-462 (Metronidazole Extended Release Tablets, 750 mg) for which the Method Validation Package has already been sent to the FDA analytical laboratory. The Method Validation Package will not be sent for this drug product.

B. Description of How the Drug Product is Intended to be Used

Treatment of women with Bacterial Vaginosis (BV).

C. Basis for Approvability or Not-Approval Recommendation

There are CMC deficiencies

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Benjamin Lim, Ph.D./11/18/2002 3/3/03
Shing Liu, Ph.D./
Wanda Pamphile, PM/

C. CC Block

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of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #1

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-505 APPLICANT: Able Laboratories, Inc.

DRUG PRODUCT: Metronidazole Capsules, 375 mg

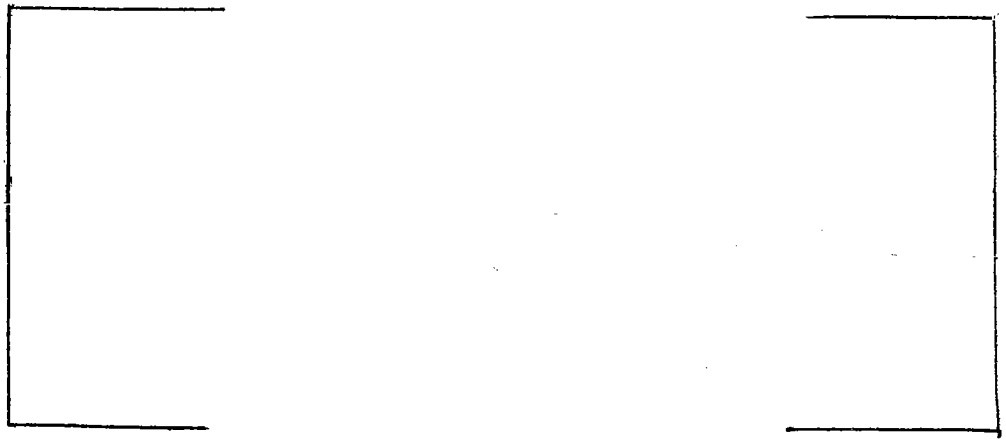
The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1.

2.

3.



B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The bioequivalence portion and the labeling portion of your submission are under review. Deficiencies, if any, will be communicated to you under separate cover.

2. The firms referenced in your application must be in compliance with cGMP at the time of approval.

3. Please provide any available drug product room temperature stability data.

4. The USP method for the drug substance and the drug product are the regulatory methods and they will prevail in the event of any dispute.

5. Please refrain from submitting testing data that are not relevant to the application, such as containers permeability test results for bottles not used for packaging Metronidazole Capsules, 375 mg.

Sincerely yours,

3/4/03

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc: ANDA 76-505
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-620 /Benjamin Lim, Ph.D. 3/3/03
HFD-620 /Shing Liu, Ph.D. / S.H. Liu 3/3/03
HFD-617 /Wanda Pamphile, PM/

F/T by

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TYPE OF LETTER: NOT APPROVABLE - MINOR

APPEARS THIS WAY
ON ORIGINAL

ANDA 76-505

Metronidazole Capsules, 375 mg

Able Laboratories, Inc.

Benjamin Lim, Ph.D.
Division of Chemistry I

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-505

2. REVIEW #: 2

3. REVIEW DATE: September 30, 2003

4. REVIEWER: Benjamin Lim, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
FIRM	
Original Submission (Acceptable for filing September 27, 2002)	September 26, 2002
AGENCY	
FDA (DBE) letter	December 11, 2001
FDA Acknowledgment letter	October 30, 2002
Original Submission	September 26, 2002
Gratuitous Amendment (container/closure testing)	November 19, 2002
Gratuitous Amendment (editorial correction)	December 20, 2002

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor Amendment	March 19, 2003
Labeling Amendment	March 28, 2003
Telephone Amendment	May 12, 2003
Telephone Amendment (Addendum)	May 13, 2003
Labeling Amendment	May 20, 2003

7. NAME & ADDRESS OF APPLICANT:

Name: Able Laboratories, Inc.

Address: 6 Hollywood Court, CN1013
South Plainfield, NJ 07080-4295

Chemistry Review Data Sheet

Representative: Shashikant Shah, R.Ph.

Telephone: (908) 754-2253

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Metronidazole Capsules

9. LEGAL BASIS FOR SUBMISSION:

a. The basis for Able Laboratories, Inc.'s proposed ANDA for Metronidazole Capsules, 375 mg is the approved, reference listed drug Flagyl 375 (metronidazole capsules, 375 mg), the subject of NDA #20-334, approved May 3, 1995, held by GD Searle LLC.

b. According to the information published in the Electronic Orange Book, Approved Drug Products with Therapeutic Equivalence Evaluations, there is no patent or exclusivity listed for this drug product.

10. PHARMACOL. CATEGORY: Antibacterial Agents

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 375 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

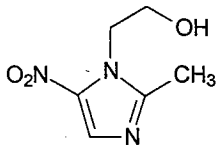
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Metronidazole. 1*H*-Imidazole-1-ethanol, 2-methyl-5-nitro-. $C_6H_9N_3O_3$. 171.16. 443-48-1.



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
—	II	—	—	3	Adequate	6/26/2003	Reviewed by B. Lim
13 DMFs	III	See Item 26	—	4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	6/24/03	S. Adams (HFD-322)
Methods Validation	N/A		
Labeling	Acceptable	6/12/03	Ruby Wu
Bioequivalence	Acceptable	9/26/03	H. Nguyen

EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes __X__ No If no, explain reason(s) below: Minor Amendment

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for ANDA 76-505

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not applicable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Able's proposed drug product, Metronidazole Capsules, 375 mg, is based on the listed reference drug, FLAGYL 375 (metronidazole capsules, 375 mg), of G.D. Searle LLC (NDA #20-334). Able's drug product is off white to light yellow powder filled in #1 capsules, opaque yellow cap imprinted "A" and opaque grey body imprinted "353" in black ink. Able's Metronidazole Capsules, 375 mg is packaged in HDPE bottles of 30, 50, 100, 500 and 1000 capsules.

Metronidazole, USP drug substance is a white to pale yellow crystals or crystalline powder. The drug substance used by Able is manufactured by [redacted] and the DMF #[redacted] referenced for the drug substance was found adequate by Benjamin Lim on 6/26/2003.

Metronidazole Capsules, 375 mg is not a USP compendial item but the proposed [redacted] assay methods are exactly the same as the methods provided in Able's ANDA 76-462 (Metronidazole Extended Release Tablets, 750 mg) for which the Method Validation Package has already been sent to the FDA analytical laboratory. The Method Validation Package will not be sent for this drug product.

B. Description of How the Drug Product is Intended to be Used

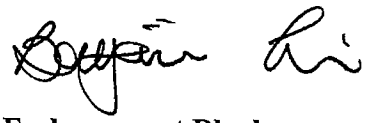
Treatment of women with Bacterial Vaginosis (BV).

C. Basis for Approvability or Not-Approval Recommendation

Applicant has satisfactorily addressed all the chemistry issues related to the drug substance, drug product and stability specifications. Bioequivalence, labeling and establishment are approvable (see Item 18 on page 5).

III. Administrative

A. Reviewer's Signature



B. Endorsement Block

Benjamin Lim, Ph.D./10/14/03 Ben Lim 10/14/03
Shing Liu, Ph.D./10/14/03 S.H.Liu 10/14/03
Wanda Pamphile, Pharm. D./ WP 10/14/03

C. CC Block

Redacted 7 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW # 2

cc: ANDA 76-505
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-620 /Benjamin Lim, Ph.D./ 10/14/03
HFD-620 /Shing Liu, Ph.D./ S.H. Liu 10/14/03
HFD-617 /Wanda Pamphile, Pharm.D./ 10/14/03

F/T by

V:\FIRMSAM\ABLE\LTRS&REV\76505.CR02.doc

TYPE OF LETTER: APPROVABLE

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-505

BIOEQUIVALENCE REVIEW(S)

FEB 11 2003

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-505
Drug Product Name	Metronidazole Capsules
Strength	375 mg
Applicant Name	Able Laboratories
Address	South Plainfield, NJ
Submission Date(s)	September 26, 2002
Amendment Date(s)	N/A
Reviewer	Hoainhon Nguyen
File Location	c:\firmsam\able\ltrs&rev\76505n0902.doc

I. Executive Summary

The firm has submitted a single-dose fasting bioequivalence study, a single-dose nonfasting bioequivalence study and dissolution data comparing the above test product with the RLD product, FLAGYL 375 capsule, manufactured by G.D. Searle. The studies and dissolution data were found acceptable. The submitted formulation of the test product was found acceptable. The test product is deemed bioequivalent to the RLD product under fasting and nonfasting conditions.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product Able's Metronidazole Capsules, 375 mg Lot# TB-146
Reference Product FLAGYL (NDA # 20-334, GD Searle LLC, Approved 05/03/95) Lot # C100882
Indication indicated in the treatment of asymptomatic trichomoniasis in females and males when the presence of the trichomonad has been confirmed by appropriate laboratory procedures (wet smears and/or cultures).

PK/PD Information

Bioavailability (systemic): 100%

Metabolism: Metabolized extensively in the liver (60%) by hydroxylation, side-chain oxidation and glucuronidation. 30% of the total systemic clearance of the drug is due to formation of hydroxymethyl-metronidazole (HMM) which possesses 30 –65% of the antibacterial activity of the parent drug. Other metabolites are not known to be active.

Half Life: 8 hours, with major route of elimination being urine excretion (60-80% of the dose)

Tmax: 2-3 hours

Excretion: mainly via urine excretion (60-80% of the dose); also fecal excretion (6-15%)

Food Effect: The extent of absorption (AUC (0-Infinity) is not affected; CMAX is decreased by 20% and TMAX is increased by 3 times.

Relevant DBE History: This is the **First Generic** product. There was no submission on metronidazole capsules previously.

Agency Guidance: According to the general BA/BE guidance, only metabolite that is formed presystemically should be measured. The active metabolite of metronidazole appears to form post-systemically. Therefore, the BE of the drug product is based on the parent drug data only. In addition, PK studies submitted under NDA 20-334 were based on plasma levels of the parent compound only.

B. Contents of Submission

		How many?
Single-dose fasting study	X	1
Single-dose fed study	X	1
In vitro dissolution testing	X	1
Waiver requests	☐	N/A

C. Bioanalytical Method Validation (Pre-Study, Vol. C1.2 Pages. 124-158)

Number of analytes	1
	Parent
Analyte name	Metronidazole
Internal Standard	beta-hydroxyethyl-theophylline
Method description	
QC range	300 to 20,000 ng/mL
Standard curve range	100 to 25,000 ng/mL
Limit of quantitation	100 ng/mL
Average recovery of Drug (%)	86.1%
Average Recovery of Int. Std (%)	89.8%
Intraday precision range (%)	1.30-3.14%
Intraday accuracy range (%)	100.7-104.8%
Interday precision range (%)	1.14-3.02%
Interday accuracy range (%)	105.4-106.5%

Bench-top stability (hrs)	5 hours	
Stock stability (days)	1 day	
Processed stability (hrs)	53 hours	
Freeze-thaw stability (cycles)	4 cycles	
Long-term storage stability (days)	101 days	
Dilution integrity	3:1 – 1:3	
	98.4% - 102.4%	
Specificity	Acceptable	
SOPs submitted	Yes	
Bioanalytical method is acceptable	Yes	
20% Chromatograms included	Yes	Serially Selected? Yes

D. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Study No.	R01-695			
Study Design	randomized, 2-way crossover			
No. of subjects enrolled	38 (36 plus 2 alternates)			
No. of subjects completing	38			
No. of subjects analyzed	36			
Subjects				
Sex(es) included (how many?)	Male	21	Female	15
Test product	Able's Metronidazole Capsules, 375 mg, Lot # TB-146			
Reference product	Searle's FLAGYL Capsules, 375 mg			
Strength tested	375 mg			
Dose	375 mg			

Summary of Statistical Analysis

Parameter	Point Estimate	90% Confidence Interval
LAUCt	102.2	99.8-104.6
LAUCi	102.1	99.8-104.5
Lcmax	107.0	103.1-111.0

The study is acceptable

2. Single-dose Fed Bioequivalence Study

Study No.	R01-696			
Study Design	randomized, 2-way crossover			
No. of subjects enrolled	24			
No. of subjects completing	23			
No. of subjects with samples analyzed	23			
Subjects				
Sex(es) included (how many)	Male	19	Female	4
Test product	Able's Metronidazole Capsules, 375 mg, Lot # TB-146			
Reference product	Searle's FLAGYL Capsules, 375 mg			
Strength tested	375 mg			
Dose	375 mg			

Summary of Statistical Analysis:

Parameter	Point Estimate	90% Confidence Interval
AUCt	103.6	100.7-106.5
AUCi	103.5	100.7-106.3
Cmax	103.0	100.4-105.7

The study is acceptable

E. Formulation

The test product formulation is shown in the Appendix.
Inactive Ingredients within IIG limits Yes
The formulation is acceptable Yes

F. In Vitro Dissolution

Methods Submitted FDA's Method
Medium 0.1 N HCl
Volume (mL) 900 mL
USP Apparatus Type I (basket)
Rotation (rpm) 100
FDA-recommended specifications —% dissolved in 30 minutes
F2- value (s): not determined due to fast dissolution rate
In vitro dissolution is acceptable

G. Waiver Request N/A

H. Deficiency Comments

I. Recommendations

1. The single-dose, fasting bioequivalence study and the single-dose nonfasting bioequivalence study conducted by Able Laboratories on the test product, Metronidazole Capsules, 375 mg, lot # TB-146, comparing it with the reference product, G.D. Searle's FLAGYL 375 capsules, lot # C100882, have been found **acceptable** by the Division of Bioequivalence. The test product, Able's Metronidazole Capsules, 375 mg, is deemed bioequivalent to the reference product, G.D. Searle's FLAGYL 375 capsules, 375 mg, under fasting and nonfasting conditions.

2. The in-vitro dissolution testing conducted by Able Laboratories on its Metronidazole Capsules, 375 mg, has been found acceptable.

The dissolution testing should be incorporated by the firm into its manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of 0.1 NHCl at 37°C using USP apparatus I(basket) at 100 rpm. The test product should meet the following specifications:

Not less than —% of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

2/11/03
Hoainhon Nguyen, Review Branch I

2/11/2003
Yih Chain Huang
Team Leader, Review Branch I

for Barbara Myers Davit

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

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IV. Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study (R01-695): A Relative Bioavailability Study of 375 mg Metronidazole Capsules Under Fasting Conditions

Study Information

Study Number R01-695
Clinical Site [redacted]
Principal Investigator [redacted], M.D.
Study/Dosing Dates 06/23/02 to 07/02/02
Analytical Site [redacted]
Analytical Director [redacted], M.S.
Analysis Dates 07/03/02 to 07/10/02
Storage Period 17 days (between the day the first sample was collected and the day the last sample was analyzed).

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Metronidazole Capsules	FLAGYL Capsules
Manufacturer	Able	Searle
Batch/Lot No.	TB-146	C100882
Manufacture Date	06/02	
Expiration Date		07/03
Strength	375 mg	375 mg
Dosage Form	Capsules	Capsules
Batch Size	[redacted]	
Potency	101.9%	99.7%
Content Uniformity	100.9% (RSD=0.4%)	100.5% (RSD=1.2%)
Formulation	See Appendix	
Dose Administered	375 mg	375 mg
Route of Administration	Oral	Oral

No. of Sequences	2		
No. of Periods	2		
No. of Treatments	2	**Balanced**	yes
No. of Groups/Sequence	1	**Washout Period**	7 days
Randomization Scheme	Yes		
Blood Sampling Times	Predose, 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48 hours		
Blood Volume Collected/Sample	10 mL/sample		
Blood Sample Processing/Storage	In EDTA vacutainers, plasma separated after centrifuging, and stored at –20C		

IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See below
Length of Fasting	10 hours predose until 4 hours postdose
Length of Confinement	10 hours predose until 24 hours postdose
Safety Monitoring	Vital signs (sitting blood pressure and radial heart rate) measured prior to dosing and at 12 and 24 hours postdose.

Subjects Demographics

Age		Age Groups		Gender		Race		Weight	
		Range	%	Sex	%	Category	%		
		<18	0			Caucasian	87		
Mean	23.7	18-40	92	Male	61	Afr. Amer.	0	Mean	73.2
SD	7.1	41-64	8	Female	39	Hispanic	8	SD	8.7
Range	18-48	65-75	0			Asian	0	Range	58-95
		>75	0			Others	5		

Study Results

Clinical: The firm's clinical summary is provided on Pages 1003-1016, Vol. C1.4

Dropout Information No dropouts

Adverse Events

Total events possibly/probably drug related: 8 (diarrhea, fatigue, headache)
received Treatment A: 1
received Treatment B: 7
All others unrelated to study medication: 12
For additional information see Vol. C1.4, pages # 1145-1146

Protocol Deviations

Deviations in blood sampling times: 31 samples with deviated sampling times (not greater than ±10 minutes except for 2 samples) PK analysis was based on actual sampling times.

Other Deviations: Repeat measurements were requested for 5 subjects. Hematology laboratory test results were outside the reference range at screening for 9 subjects, and at exit for 6 subjects. Chemistry laboratory test results were outside the reference range at screening for 14 subjects, and at exit for 9 subjects. None of the above deviations were judged clinically significant by the study investigator.

Comments: None of the above adverse events or protocol deviations were judged clinically significant by the study investigator.

QC Conc. (ug/mL)	.300	12.50	20.00
Inter day Precision (%CV)	3.8 (n=51)	3.3 (n=51)	4.0 (n=51)
Inter day Accuracy (% Accuracy)	98.7 (n=51)	100.1 (n=51)	99.8 (n=51)
Cal. Standards Conc. (ug/mL)	0.100, 0.500, 1.00, 3.00, 6.00, 12.5, 25.0		
Inter day Precision (%CV)	1.34-5.83		
Inter day Accuracy (% Accuracy)	97.7-105.3		
Long-term frozen storage stability (if applicable)	See prestudy stability data (pages 2-3)		
Linearity Range (range of R^2 values)	0.9984-0.9998		
Linearity Range (ug/mL)	0.100-25.0		

Repeat Assays:

SOPs (Vol. C1.2, Pages 196-198) The SOP #PA 098.1 specified analytical reasons for reassaying or reinjecting of samples.
Number of Samples Re-assayed: 2 (for analytical reasons)
Number of Pharmacokinetic Repeats: None
Impact of Repeat-assays on the study outcome: None

Chromatograms: No interfering peaks observed.

Comments: (on analytical study) The highest observed CMAX was 11.98 ug/mL. Selection of concentration range of QCs and standard curves was therefore acceptable.

Conclusion: Analytical method is acceptable.

Pharmacokinetic/Statistical Analysis

Mean Plasma Concentrations Table #1, Figure #1 (Attachments)
AUCt/AUCi ratio Tables # 2& 3 (Attachments)

Mean Pharmacokinetic Parameters and 90% Confidence Intervals:

A. Arithmetic Mean Pharmacokinetic Parameters

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC0-t	ug.hr/mL	90.785	18	89.035	19	1.02
AUCi	ug.hr/mL	93.397	18	91.516	19	1.02
Cmax	ug/mL	8.510	23	7.956	22	1.07
Tmax	Hrs	1.27	45	1.51	50	0.84
T1/2	hrs	8.21	19	8.33	20	0.99
Kel	hrs^{-1}	0.0869	16	0.0859	16	1.01

B. Geometric Mean and 90% Confidence Intervals

Parameter	Test	Reference	T/R	90% CI
	Mean	Mean		
AUC0-t	89.310	87.398	1.02	1.00,1.04
AUCi	91.766	89.849	1.02	1.00,1.04
Cmax	8.304	7.762	1.07	1.03,1.11

C. Total SD and within-subject error (root MSE): Values are shown below

(for ln-transformed AUCt and Cmax only)

	lnCmax	lnAUCt
Root MSE, test & ref combined	0.091786	0.058307

Individual Subject AUCt, AUCi and Cmax data with Per and SEQ: Tables # 4&5 (Attachments)

Comments: (on pharmacokinetic analysis)

ALWAYS include the comments below. Other comments may be listed if appropriate.

- Ke and AUCi were determined for all subjects.
- Indicate the number of subjects with the following:
  a. measurable drug concentrations at 0 hr: None
  b. first scheduled post-dose sampling time as Tmax: None
  c. first measurable drug concentration as Cmax: None
- Did pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations: Yes. Reviewer's 90% CI for lnAUCT, lnAUCI and lnCMAX were [1.00,1.05], [1.00,1.04], and [1.03,1.11], respectively.
- Were there statistically significant sequence or period effects? No
- Are the 90% confidence intervals for AUCt, AUCi, Cmax within the acceptable limits of 80-125%: Yes
- If the subjects were dosed as more than one group, comment on the statistical analysis for group effect: N/A

Conclusion: The single-dose fasting bioequivalence study is acceptable.

2. Single-dose Nonfasting Bioequivalence Study (R01-696): A Relative Bioavailability Study of 375 mg Metronidazole Capsules Under Nonfasting Conditions

Study Information

Study Number R01-696
Clinical Site ———————————
Principal Investigator ———— M.D.
Study/Dosing Dates 06/30/02 to 07/09/02
Analytical Site————————
Analytical Director ————, M.S.

Analysis Dates 07/12/02 to 07/17/02
Storage Period 18 days (between the day the first sample was collected and the day the last sample was analyzed).

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Metronidazole Capsules	FLAGYL Capsules
Manufacturer	Able	Searle
Batch/Lot No.	TB-146	C100882
Manufacture Date	06/02	
Expiration Date		07/03
Strength	375 mg	375 mg
Dosage Form	Capsules	Capsules
Batch Size		
Potency	101.9%	99.7%
Content Uniformity	100.9% (RSD=0.4%)	100.5% (RSD=1.2%)
Formulation	See Appendix	
Dose Administered	375 mg	375 mg
Route of Administration	Oral	Oral

No. of Sequences		2	
No. of Periods		2	
No. of Treatments		2	**Balanced** yes
No. of Groups/Sequence	1		**Washout Period** 7 days
Randomization Scheme		Yes	
Blood Sampling Times		Predose, 0.50, 1, 1.50, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 16, 24, 36, 48 hours	
Blood Volume Collected/Sample		10 mL/sample	
Blood Sample Processing/Storage		In EDTA vacutainers, plasma separated after centrifuging, and stored at –20C	
IRB Approval		Yes	
Informed Consent		Yes	
Subjects Demographics		See below	
Length of Fasting		10 hours predose until a standardized breakfast 30 minutes prior to dosing	
Length of Confinement		10 hours predose until 24 hours postdose	
Safety Monitoring		Vital signs (sitting blood pressure and radial heart rate) measured prior to dosing and at 12 and 24 hours postdose.	

Subjects Demographics

Age		Age Groups		Gender		Race		Weight	
		Range	%	Sex	%	Category	%		
		<18	0			Caucasian	100		
Mean	22.6	18-40	100	Male	19	Afr. Amer.	0	Mean	76.3
SD	5.1	41-64	0	Female	5	Hispanic	0	SD	9.7
Range	18-40	65-75	0			Asian	0	Range	59-95
		>75	0			Others	0		

Study Results

Clinical: The firm's clinical summary is provided on Pages 2585-2597, Vol. C1.8

Dropout Information Subject #3 was dropped due to a positive pregnancy screen prior to Period II

Adverse Events

Total events possibly/probably drug related: None
All others unrelated to study medication: 9
For additional information see Vol. C1.8, pages # 2708-2709

Protocol Deviations

Deviations in blood sampling times: 13 samples with deviated sampling times (not greater than ±5 minutes) PK analysis was based on actual sampling times.

Other Deviations: Repeat blood pressure and heart rate measurements were requested for 1 subject. Hematology laboratory test results were outside the reference range at screening for 2 subjects, and at exit for 2 subjects. Chemistry laboratory test results were outside the reference range at screening for 5 subjects, and at exit for 6 subjects. None of the above deviations were judged clinically significant by the study investigator.
One subject was tested positive for pregnancy prior to Period II and dropped from the study.

Comments: None of the above adverse events or protocol deviations were judged clinically significant by the study investigator.

QC Conc. (ug/mL)	.300	12.50	20.00
Inter day Precision (%CV)	3.6 (n=32)	3.8 (n=32)	4.1 (n=32)
Inter day Accuracy (% Accuracy)	96.1 (n=32)	99.6 (n=32)	99.5 (n=32)
Cal. Standards Conc. (ug/mL)	0.100, 0.500, 1.00, 3.00, 6.00, 12.5, 25.0		
Inter day Precision (%CV)	1.18-2.67		
Inter day Accuracy (% Accuracy)	91.8-110.0		

Long-term frozen storage stability (if applicable)	See prestudy stability data (pages 2-3)
Linearity Range (range of R^2 values)	0.9990-0.9996
Linearity Range (ug/mL)	0.100-25.0

Repeat Assays:

SOPs (Vol. C1.6, Pages 2022-2031) The SOP #PA 098.1 specified analytical reasons for reassaying or reinjecting of samples.
Number of Samples Re-assayed: 5 (for analytical reasons)
Number of Pharmacokinetic Repeats: None
Impact of Repeat-assays on the study outcome: None

Chromatograms: No interfering peaks observed.

Comments: (on analytical study) The highest observed CMAX was 8.331 ug/mL. Therefore only the first 2 QCs (low and medium), and standard curves, were appropriate for the actual samples.

Conclusion: Analytical method is acceptable.

Pharmacokinetic/Statistical Analysis

Mean Plasma Concentrations Table #6, Figure #2 (Attachments)
AUCt/AUCi ratio Tables # 7& 8 (Attachments)

Mean Pharmacokinetic Parameters and 90% Confidence Intervals:

A. Arithmetic Mean Pharmacokinetic Parameters

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC0-t	ug.hr/mL	79.379	16	76.332	17	1.04
AUCi	ug.hr/mL	81.673	15	78.654	13	1.04
Cmax	ug/mL	6.000	18	5.802	17	1.03
Tmax	Hrs	3.26	28	3.04	28	1.07
T1/2	hrs	8.27	11	8.18	13	1.01
Kel	hrs^{-1}	0.0848	11	0.0861	13	0.98

B. Geometric Mean and 90% Confidence Intervals

Parameter	Test	Reference	T/R	90% CI
	Mean	Mean		
AUC0-t	78.283	75.587	1.04	1.01,1.06
AUCi	80.604	77.912	1.03	1.01,1.06
Cmax	5.890	5.719	1.03	1.00,1.06

C. Total SD and within-subject error (root MSE): Values are shown below (for ln-transformed AUCt and Cmax only)

	LnCmax	lnAUCt
Root MSE, test & ref combined	0.053401	0.054562

Individual Subject AUCt, AUCi and Cmax data with Per and SEQ: Tables #9&10 (Attachments)

Comments: (on pharmacokinetic analysis)

ALWAYS include the comments below. Other comments may be listed if appropriate.

- Ke and AUCi were determined for all subjects.
- Indicate the number of subjects with the following:
  d. measurable drug concentrations at 0 hr: None
  e. first scheduled post-dose sampling time as Tmax: None
  f. first measurable drug concentration as Cmax: None
- Did pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations: Yes. Reviewer's 90% CI for lnAUCT, lnAUCI and lnCMAX were[1.01;1.06]. [1.00;1.06] and [1.00;1.06], respectively.
- Were there statistically significant sequence or period effects? No
- Are the 90% confidence intervals for AUCt, AUCi, Cmax within the acceptable limits of 80-125%: Yes
- If the subjects were dosed as more than one group, comment on the statistical analysis for group effect: N/A

Conclusion: The single-dose fasting bioequivalence study is acceptable.

Dissolution Data

Sampling Time (min.)	Test Product, Able's Strength 375 mg Lot No. TB-146			Reference Product, FLAGYL 375 Strength 375 mg Lot No. C100882		
	Mean	%CV	Range	Mean	%CV	Range
10	70.8	31.7		91.4	12.0	
20	94.7	7.2		99.1	2.5	
30	100.2	2.1		99.9	1.7	
45	101.2	2.2		100.0	1.4	

B. Attachments

Table I
Comparative Mean Plasma Levels of Metronidazole
Dose=375 mg; n=36
ug/mL(CV%)
Fasting/Single-Dose Study

Hour	Test	Reference
0	0	0
0.33	3.105 (111)	1.570 (120)
0.67	5.968 (59)	5.119 (56)
1	6.885 (38)	6.644 (41)
1.33	7.203 (28)	6.864 (34)
1.67	7.380 (23)	6.928 (30)
2	7.146 (20)	6.877 (26)
2.50	6.781 (19)	6.702 (19)
3	6.342 (19)	6.376 (19)
4	5.751 (18)	5.764 (20)
6	4.585 (17)	4.561 (19)
8	3.893 (16)	3.850 (17)
12	2.804 (17)	2.776 (17)
16	2.007 (17)	1.988 (20)
24	1.149 (28)	1.138 (27)
36	0.406 (48)	0.398 (43)
48	0.133 (95)	0.138 (87)

Figure 1
Fasting Study No. R01-695

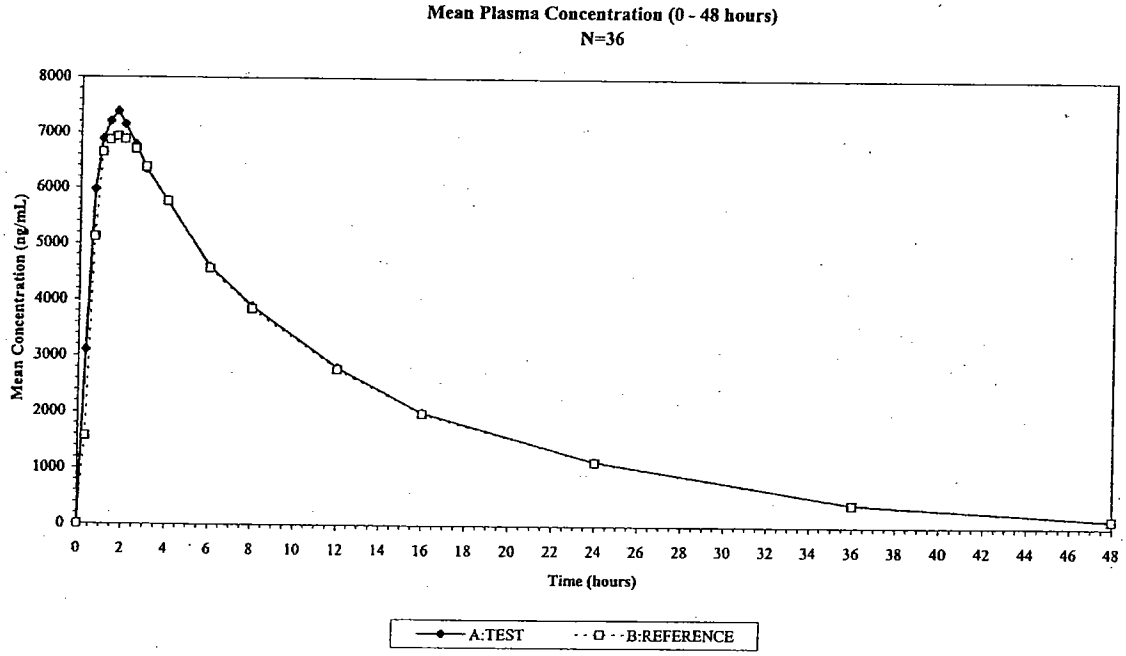

Table II

Test Product's Individual AUCT/AUCI Ratios

Fasting Study No. R01-695

Subject	Sequence	Period	AUCT (ng-hr/-L)	AUCI (ng-hr/mL)	AUCT/AUCI
1	1	1			
2	2	2			
3	1	1			
4	2	2			
5	2	2			
6	2	2			
7	2	2			
8	2	2			
9	2	2			
10	1	1			
11	2	2			
12	1	1			
13	2	2			
14	1	1			
15	1	1			
16	2	2			
17	1	1			
18	2	2			
19	1	1			
20	1	1			
21	2	2			
22	1	1			
23	1	1			
24	2	2			
25	1	1			
26	2	2			
27	1	1			
28	2	2			
29	1	1			
30	2	2			
31	1	1			
32	1	1			
33	1	1			
34	2	2			
35	2	2			
36	1	1			
N			36	36	36
MEAN			90785.17	93307.33	0.97336
STDEV			16354.13	17042.03	0.01551
% CV			18.01	18.26	1.59310
MIN					
MAX					

Table III
Reference Product's Individual AUCT/AUCI Ratios
Fasting Study No. R01-695

Subject	Sequence	Period	AUCT (ng-hr/mL)	AUCI (ng-hr/mL)	AUCT/AUCI
1	1	2			
2	2	1			
3	1	2			
4	2	1			
5	2	1			
6	2	1			
7	2	1			
8	2	1			
9	2	1			
10	1	2			
11	2	1			
12	1	2			
13	2	1			
14	1	2			
15	1	2			
16	2	1			
17	1	2			
18	2	1			
19	1	2			
20	1	2			
21	2	1			
22	1	2			
23	1	2			
24	2	1			
25	1	2			
26	2	1			
27	1	2			
28	2	1			
29	1	2			
30	2	1			
31	1	2			
32	1	2			
33	1	2			
34	2	1			
35	2	1			
36	1	2			
N			36	36	36
MEAN			89035.42	91516.08	0.97289
STDEV			17168.41	17661.93	0.01798
% CV			19.28	19.30	1.85
MIN					
MAX					

Table IV

Fasting Study No. R01-695

Individual Pharmacokinetic Parameters - Test Product

Subject	Sequence	Period	Product	T_{max} (hr)	C_{max} (ng/mL)	AUC_{0-t} (ng-hr/mL)	k_{elim} (1/hr)	$t_{1/2}$ (hr)	AUC_{inf} (ng-hr/mL)	Ln-Transformed C_{max}	Ln-Transformed AUC_{0-t}	Ln-Transformed AUC_{inf}
1	1	1	A:TEST									
2	2	2	A:TEST									
3	1	1	A:TEST									
4	2	2	A:TEST									
5	2	2	A:TEST									
6	2	2	A:TEST									
7	2	2	A:TEST									
8	2	2	A:TEST									
9	2	2	A:TEST									
10	1	1	A:TEST									
11	2	2	A:TEST									
12	1	1	A:TEST									
13	2	2	A:TEST									
14	1	1	A:TEST									
15	1	1	A:TEST									
16	2	2	A:TEST									
17	1	1	A:TEST									
18	2	2	A:TEST									
19	1	1	A:TEST									
20	1	1	A:TEST									
21	2	2	A:TEST									
22	1	1	A:TEST									
23	1	1	A:TEST									
24	2	2	A:TEST									
25	1	1	A:TEST									
26	2	2	A:TEST									
27	1	1	A:TEST									
28	2	2	A:TEST									
29	1	1	A:TEST									
30	2	2	A:TEST									
31	1	1	A:TEST									
32	1	1	A:TEST									
33	1	1	A:TEST									
34	2	2	A:TEST									
35	2	2	A:TEST									
36	1	1	A:TEST									
N				36	36	36	36	36	36	36	36	36
MEAN				1.27	8510.18	90785.17	0.0869	8.21	93307.33	9.024	11.400	11.427
STDEV				0.57	1926.68	16354.13	0.01	1.54	17042.03	0.22	0.19	0.19
% CV				45.25	22.64	18.01	15.91	18.79	18.26	2.49	1.63	1.63
MIN												
MAX												

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Table V

Fasting Study No. R01-695

Individual Pharmacokinetic Parameters - Reference Product

Subject	Sequence	Period	Product	T_{max} (hr)	C_{max} (ng/mL)	AUC_{0-t} (ng-hr/mL)	k_{elm} (1/hr)	$t_{1/2}$ (hr)	AUC_{inf} (ng-hr/mL)	Ln-Transformed C_{max}	Ln-Transformed AUC_{0-t}	Ln-Transformed AUC_{inf}
1	1	2	B:REFERENCE									
2	2	1	B:REFERENCE									
3	1	2	B:REFERENCE									
4	2	1	B:REFERENCE									
5	2	1	B:REFERENCE									
6	2	1	B:REFERENCE									
7	2	1	B:REFERENCE									
8	2	1	B:REFERENCE									
9	2	1	B:REFERENCE									
10	1	2	B:REFERENCE									
11	2	1	B:REFERENCE									
12	1	2	B:REFERENCE									
13	2	1	B:REFERENCE									
14	1	2	B:REFERENCE									
15	1	2	B:REFERENCE									
16	2	1	B:REFERENCE									
17	1	2	B:REFERENCE									
18	2	1	B:REFERENCE									
19	1	2	B:REFERENCE									
20	1	2	B:REFERENCE									
21	2	1	B:REFERENCE									
22	1	2	B:REFERENCE									
23	1	2	B:REFERENCE									
24	2	1	B:REFERENCE									
25	1	2	B:REFERENCE									
26	2	1	B:REFERENCE									
27	1	2	B:REFERENCE									
28	2	1	B:REFERENCE									
29	1	2	B:REFERENCE									
30	2	1	B:REFERENCE									
31	1	2	B:REFERENCE									
32	1	2	B:REFERENCE									
33	1	2	B:REFERENCE									
34	2	1	B:REFERENCE									
35	2	1	B:REFERENCE									
36	1	2	B:REFERENCE									
N				36	36	36	36	36	36	36	36	36
MEAN				1.51	7955.70	89035.42	0.0859	8.33	91516.08	8.957	11.378	11.406
STDEV				0.76	1785.99	17168.41	0.01	1.65	17661.93	0.23	0.20	0.20
% CV				50.11	22.45	19.28	16.39	19.86	19.30	2.52	1.73	1.71
MIN												
MAX												

APPEARS THIS WAY
ON ORIGINAL

Table VI
Comparative Mean Plasma Levels of Metronidazole
Dose=375 mg; n=23
ug/mL(CV%)
Nonfasting/Single-Dose Study

Hour	Test	Reference
0	0	0
0.50	0.104 (233)	0.282 (192)
1	1.036 (119)	1.458 (121)
1.50	2.587 (66)	3.092 (62)
2	4.064 (47)	4.288 (45)
2.50	5.081 (34)	5.105 (35)
3	5.372 (27)	5.240 (23)
3.50	5.427 (19)	5.285 (17)
4	5.421 (16)	5.284 (14)
4.50	5.247 (17)	5.073 (14)
5	5.095 (18)	4.862 (15)
6	4.608 (18)	4.377 (14)
8	3.902 (17)	3.727 (14)
12	2.810 (17)	2.634 (13)
16	2.009 (16)	1.894 (14)
24	1.155 (19)	1.105 (20)
36	0.387 (29)	0.358 (33)
48	0.120 (70)	0.110 (85)

Figure 2
Nonfasting Study No. R01-696

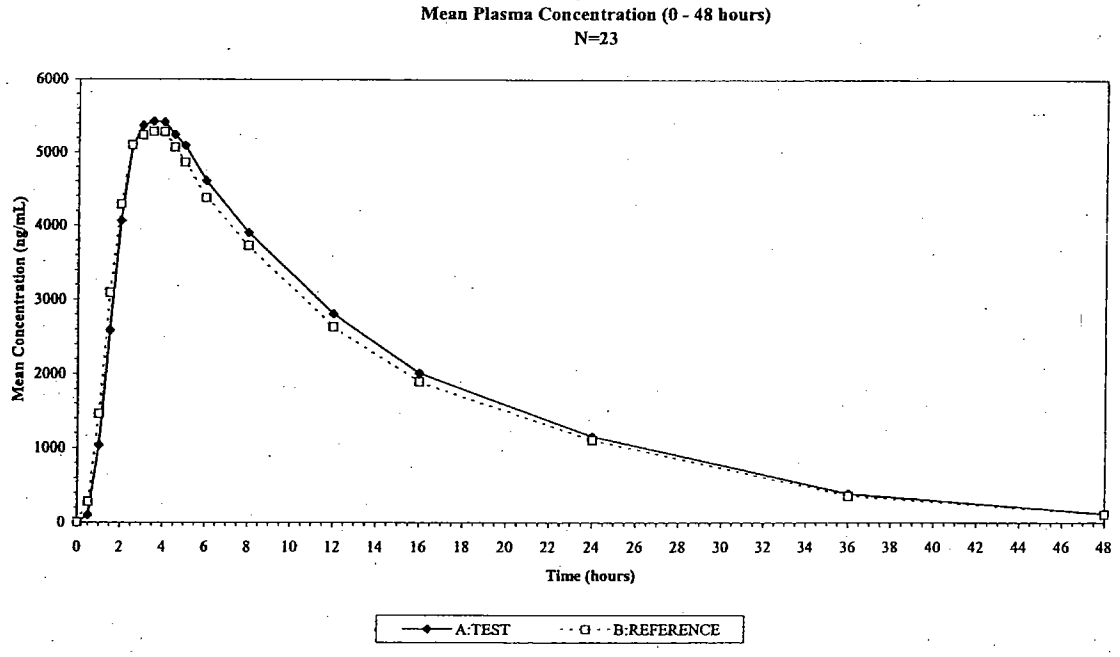

Table VII

Test Product's Individual AUCT/AUCI Ratios

Nonfasting Study No. R01-696

Subject	Sequence	Period	AUCT	AUCI	AUCT/AUCI
1	2	2			
2	2	2			
4	1	1			
5	1	1			
6	2	2			
7	2	2			
8	2	2			
9	1	1			
10	1	1			
11	1	1			
12	2	2			
13	2	2			
14	1	1			
15	2	2			
16	1	1			
17	2	2			
18	2	2			
19	1	1			
20	2	2			
21	2	2			
22	1	1			
23	1	1			
24	1	1			
N			23	23	23
MEAN			79379.04	81672.61	0.971326
SDEV			12453.86	12425.39	0.011720
CV%			15.69	15.21	1.21
MIN					
MAX					

Table VIII
Reference Product's Individual AUCT/AUCI Ratios
Nonfasting Study No. R01-696

Subject	Sequence	Period	AUCT	AUCI	AUCT/AUCI
1	2	1			
2	2	1			
4	1	2			
5	1	2			
6	2	1			
7	2	1			
8	2	1			
9	1	2			
10	1	2			
11	1	2			
12	2	1			
13	2	1			
14	1	2			
15	2	1			
16	1	2			
17	2	1			
18	2	1			
19	1	2			
20	2	1			
21	2	1			
22	1	2			
23	1	2			
24	1	2			
N			23	23	23
MEAN			76332.43	78654.30	0.97022
STDEV			10408.79	10447.50	0.01160
% CV			13.64	13.28	1.20
MIN					
MAX					

Table IX

Fasting Study No. R01-696

Individual Pharmacokinetic Parameters - Test Product

Subject	Sequence	Period	Product	T_{max} (hr)	C_{max} (ng/mL)	AUC_{0-t} (ng-hr/mL)	k_{elim} (1/hr)	$t_{1/2}$ (hr)	AUC_{inf} (ng-hr/mL)	Ln-Transformed C_{max}	Ln-Transformed AUC_{0-t}	Ln-Transformed AUC_{inf}
1	2	2	A:TEST									
2	2	2	A:TEST									
4	1	1	A:TEST									
5	1	1	A:TEST									
6	2	2	A:TEST									
7	2	2	A:TEST									
8	2	2	A:TEST									
9	1	1	A:TEST									
10	1	1	A:TEST									
11	1	1	A:TEST									
12	2	2	A:TEST									
13	2	2	A:TEST									
14	1	1	A:TEST									
15	2	2	A:TEST									
16	1	1	A:TEST									
17	2	2	A:TEST									
18	2	2	A:TEST									
19	1	1	A:TEST									
20	2	2	A:TEST									
21	2	2	A:TEST									
22	1	1	A:TEST									
23	1	1	A:TEST									
24	1	1	A:TEST									
N				23	23	23	23	23	23	23	23	23
MEAN				3.26	6000.44	79379.04	0.0848	8.27	81672.61	8.683	11.271	11.300
STDEV				0.90	1097.35	12453.86	0.01	0.92	12425.39	0.18	0.15	0.15
% CV				27.67	18.29	15.69	10.85	11.18	15.21	2.13	1.36	1.31
MIN												
MAX												

APPEARS THIS WAY
ON ORIGINAL

Table X

Nonfasting Study No. R01-696

Individual Pharmacokinetic Parameters - Reference Product

Subject	Sequence	Period	Product	T_{max} (hr)	C_{max} (ng/mL)	AUC_{0-t} (ng-hr/mL)	k_{elim} (1/hr)	$t_{1/2}$ (hr)	AUC_{inf} (ng-hr/mL)	Ln-Transformed C_{max}	Ln-Transformed AUC_{0-t}	Ln-Transformed AUC_{inf}
1	2	1	B:REFERENCE									
2	2	1	B:REFERENCE									
4	1	2	B:REFERENCE									
5	1	2	B:REFERENCE									
6	2	1	B:REFERENCE									
7	2	1	B:REFERENCE									
8	2	1	B:REFERENCE									
9	1	2	B:REFERENCE									
10	1	2	B:REFERENCE									
11	1	2	B:REFERENCE									
12	2	1	B:REFERENCE									
13	2	1	B:REFERENCE									
14	1	2	B:REFERENCE									
15	2	1	B:REFERENCE									
16	1	2	B:REFERENCE									
17	2	1	B:REFERENCE									
18	2	1	B:REFERENCE									
19	1	2	B:REFERENCE									
20	2	1	B:REFERENCE									
21	2	1	B:REFERENCE									
22	1	2	B:REFERENCE									
23	1	2	B:REFERENCE									
24	1	2	B:REFERENCE									
N				23	23	23	23	23	23	23	23	23
MEAN				3.04	5801.78	76332.43	0.0861	8.18	78654.30	8.653	11.234	11.265
STDEV				0.85	975.37	10408.79	0.01	1.10	10447.50	0.16	0.13	0.13
% CV				27.98	16.81	13.64	13.23	13.45	13.28	1.90	1.17	1.15
MIN												
MAX												

APPEARS THIS WAY
ON ORIGINAL

Table XI

Formulation of Able's Metronidazole Capsules, 375 mg

Ingredients	Code #	mg/capsule	% w/w	Pharmaceutical Function
Metronidazole, USP	[redacted]	375.00	[redacted]	[redacted]
Starch NF (Corn)	[redacted]			
Magnesium Stearate, NF				
#1 Capsules, Opaque Yellow cap / Opaque Gray Body imprinted "A353" in black ink				
*Capsule consisting of : Black Iron Oxide D&C Red #33 D&C Yellow #10 Gelatin Titanium Dioxide *Black Ink consisting of : Black [redacted] Pharmaceutical Glaze Black Iron Oxide Alcohol Propylene Glycol FD&C Blue # 2 FD&C Red # 40 FD&C Blue # 1 D&C Yellow # 10 Black [redacted] Pharmaceutical Glaze Black Iron Oxide Alcohol FD&C Blue # 2 FD&C Red # 40 FD&C Blue # 1 D&C Yellow # 10	[redacted]	[redacted]	[redacted]	[redacted]
Total		485.00	100%	

APPEARS THIS WAY ON ORIGINAL

BIOEQUIVALENCY COMMENTS

ANDA: 76-505 APPLICANT: Able Laboratories

DRUG PRODUCT: Metronidazole Capsules, 375 mg.

The Division of Bioequivalence has completed its review and has no further questions at this time.

In future applications, please include the address of the laboratories conducting the dissolution testing in the bioequivalence section of the ANDA.

We acknowledge the following dissolution testing has been incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of 0.1 N HCl, at 37C using USP Apparatus I(basket) at 100 rpm. The test product should meet the following specifications:

> Not less than —% (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

In the future, for the assay validation, please select QC concentrations that are within the concentration range of the actual study samples.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

for Barbara M. Scott

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC:ANDA 76-505
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-652/ Bio Secretary - Bio Drug File
HFD-652/ HNguyen
HFD-652/ YHuang

Endorsements: (Final with Dates)
HFD-652/ HNguyen
HFD-652/ YHuang 2/11/2003
HFD-617/ A. Sigler
for HFD-650/ D. Conner 2/20/03

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Printed in final on / /

BIOEQUIVALENCY - ACCEPTABLE Submission date: 09-26-02

1. FASTING STUDY (STF) o/c Strength: 375 MG
Clinical: _____ **Outcome: AC**
Analytical: _____

2. NON-FASTING STUDY (STP) o/c Strength: 375 MG
Clinical: _____ **Outcome: AC**
Analytical: _____

OUTCOME DECISIONS: **IC** - Incomplete **UN** - Unacceptable (fatal flaw)
AC - Acceptable

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 76-505 SPONSOR : Able Laboratories
DRUG AND DOSAGE FORM : Metronidazole Capsules
STRENGTH(S) : 375 mg
TYPES OF STUDIES : Fasting Study & Non-Fasting Study
CINICAL STUDY SITE(S) ———
ANALYTICAL SITE(S) : ———

STUDY SUMMARY : Acceptable
DISSOLUTION : Acceptable
WAIVER REQUEST: N/A

DSI INSPECTION STATUS

Inspection needed: YES	Inspection status:	Inspection results: Satisfactory Received 11/13/02 from Strazzullo Request
First Generic YES	Inspection requested: (date)	
New facility ____	Inspection completed: (date)	11/13/03
For cause ____		
Other ____		

PRIMARY REVIEWER : Hoainhon Nguyen BRANCH : I
INITIAL : HNe DATE : 2/11/03

TEAM LEADER : Yih-Chain Huang BRANCH : I
INITIAL : YCH DATE : 2/11/2003

for DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.
INITIAL : Barbara M Davit DATE : 9/26/03

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-505

ADMINISTRATIVE DOCUMENTS

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE : October 7, 2002

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615) 07-OCT-2002

SUBJECT: Examination of the bioequivalence study submitted with an ANDA for Metronidazole Capsules, 375 mg to determine if the application is substantially complete for filing.

Able Laboratories, Inc. has submitted ANDA 76-505 for Metronidazole Capsules, 375 mg. The ANDA contains a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the for study submitted by Able on September 26, 2002 for its Metronidazole product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

2

BIOEQUIVALENCE CHECKLIST FOR APPLICATION COMPLETENESS
First Generic ANDA

ANDA# 76-505 FIRM NAME ABLE LABORATORIES, INC

DRUG NAME METRONIDAZOLE CAPSULES, 375 MG

DOSAGE FORM ORAL CAPSULES

Requested by: _____
Chief, Regulatory Support Team, (HFD-615)

Summary of Findings by Division of Bioequivalence

☒ **Study meets statutory requirements**

☐ **Study does NOT meet statutory requirements**
Reason:

☐ **Waiver meets statutory requirements**

☐ **Waiver does NOT meet statutory requirements**
Reason:

RECOMMENDATION: ✔ COMPLETE ___ INCOMPLETE

Reviewed by:

Patrick Nwakama, Pharm.D. Date: 10/10/2002
Reviewer

Gur Jai Pal Singh, Ph.D. Date: 10-14-02
Team Leader

Dale P. Conner, Pharm.D. Date: 10/15/02
Director, Division of Bioequivalence

Item Verified:	Yes	No	Required Amount	Amount Sent	Comments
Protocol	X				Fasting & Fed Studies
Assay Methodology	X				
Procedure SOP	X				
Methods Validation	X				
Study Results Ln/Lin	X				
Adverse Events	X				
IRB Approval	X				
Dissolution Data	X				
Pre-screening of Patients	X				
Chromatograms	X				
Consent Forms	X				
Composition	X				
Summary of Study	X				
Individual Data & Graphs, Linear & Ln	X				
PK/PD Data Disk (or Elec Subm)	X				
Randomization Schedule	X				
Protocol Deviations	X				
Clinical Site	X				
Analytical Site	X				
Study Investigators	X				
Medical Records	X				
Clinical Raw Data	X				
Test Article Inventory	X				

BIO Batch Size	X				—
Assay of Active Content Drug	X				99.5%
Content Uniformity	X				100.3%
Date of Manufacture	X				06/02
Exp. Date of RLD	X				07/03
BioStudy Lot Numbers	X				TEST - TB-146 REF - C100882
Statistics	X				
Summary results provided by the firm indicate studies pass BE criteria	X				
Waiver requests for other strengths / supporting data		X			ONLY ONE STRENGTH (375 MG)

Additional Comments regarding the ANDA:

APPEARS THIS WAY
ON ORIGINAL

Created PDF Form:BIO CHKLST.PDF 05/15/02

RECORD OF TELEPHONE CONVERSATION

Reference is made to minor amendments dated March 19, 2003 and March 20, 2003 for ANDA's 76-505 and 76-519 respectively.

Reference is also made to ANDA 76-462 for Metronidazole Extended-release Tablets, 750 mg.

FDA: Based on your Extented-release product, you gave limits for the drug product release Related Substances and stability Related Substances for Metronidazole. We need consistency within all of the applications. Please give us a limit for the tablets (ANDA 76-519) and capsules (ANDA 76-505) that is in line with the Extended-release tablets for the Related substances.

Firm: We agree to the limits as referenced in ANDA 76-462

Note: Related Substances limit obtained from ANDA 76-462 for referencing puposes.

DATE:
May 12, 2003

ANDA NUMBER

76-505/76-519

TELECON INITIATED BY
AGENCY

PRODUCT NAME:

Metronidazole Tablets
250 mg and 500 mg
& Metronidazole Capsules
375 mg

FIRM NAME:

Able Laboratories Inc.

FIRM REPRESENTATIVES:
Shashi Shah
Iva Klemick

TELEPHONE NUMBER:

908-754-2253

FDA REPRESENTATIVES
Shing, Liu, Ph.D.
Benjamin Lim, Ph.D
Wanda Pamphile, Pharm.D.

SIGNATURES:
Shing, Liu S.H.Liu 5/13/03
Benjamin Lim 5/13/03
Wanda Pamphile 5/13/03

Orig: ANDA 76-505/76-519
Cc: Division File
Chem. I Telecon Binder

V:\FIRMSAM\ABLE\LTRS&REV\76505.doc

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-505

CORRESPONDENCE

ABLE
LABORATORIES
INC.

76-505

September 26, 2002

FEDERAL EXPRESS
Dr. Gary Buehler
Director
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

505(j)(2)(A) OK
30-OCT-2002
Gregory S. Davis

ABBREVIATED NEW DRUG APPLICATION
METRONIDAZOLE CAPSULES
375 mg

Dear Dr. Buehler:

Pursuant to Section 505(j)(1) of the Federal Food, Drug and Cosmetic Act, ABLE LABORATORIES, INC., herewith submits an original Abbreviated New Drug Application (ANDA) for Metronidazole Capsules, 375 mg.

The Metronidazole Capsules, 375 mg drug product for which this ANDA is submitted is identical to GD Searle LLC's Flagyl® 375 (metronidazole capsules 375 mg), previously approved by the Food and Drug Administration under New Drug Application 020334.

It is the opinion of ABLE LABORATORIES, INC., and to the best of our knowledge, with respect to each patent which claims the listed drug or which claims a use for such listed drug for which we are seeking approval that such patent(s), if filed, have expired and therefore will not be infringed by the manufacture, use, or sale of the drug for which this Abbreviated New Drug Application is being submitted.

The firm has incorporated the Division of Bioequivelence's recommendation to conduct in-vetro dissolution testing using the FDA method. A copy of the December 2001 has been included for your reference.

In vivo bioavailability studies have been conducted on ABLE Laboratories, Inc.'s Metronidazole Capsules, 375 mg and compared to the Reference Listed Drug, GD Searle LLC's Flagyl® 375 (metronidazole capsules, 375 mg). Electronic copies of the analytical section of the bioequivalence study from ——————— have been included in Volume I.

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SEP 27 2002
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ABLE
LABORATORIES
INC.

Dissolution testing was performed on the product. The comparative drug release has been included in Section VI.3.

We are sumitting duplicate copies of *Section XV Analytical Methods* in accordance to the **Guidance for Industry Organization of an ANDA Feburary 1999 OGD # 1Revision 1.**

We are requesting a two (2) year expiration dating period for this product based on accelerated stability data provided herein. We trust that this Abbreviated New Drug Application for Metronidazole Capsules, 375 mg meets all requirements.

If you should require additional information or have any questions regarding this Abbreviated New Drug Application, please do not hesitate to contact me directly by phone at (908) 754-2253, ext. 505 or by facsimile at (908) 753-9383.

We have submitted a true copy of the chemistry section to the field.

Thank you.

Sincerely,

ABLE LABORATORIES, INC.

Mr. Shashikant Shah, R.Ph.
V.P. Quality/Regulatory

Volumes Submitted:
Archival -13
Field Copy -13
Chemistry -5
Bioequivalence -9

6 Hollywood Court ◢ CN 1013 ◢ South Plainfield ◢ New Jersey 07080 ◢ Telephone: (908) 754-ABLE ◢ Fax: (908) 754-2476
www.ablelabs.com

ANDA 76-505

OCT 30 2002

Able Laboratories, Inc.
Attention: Shashikant Shah
6 Hollywood Court, CN 1013
South Plainfield, NJ 07080-4295

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Metronidazole Capsules, 375 mg

DATE OF APPLICATION: September 26, 2002

DATE (RECEIVED) ACCEPTABLE FOR FILING: September 27, 2002

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Wanda Pamphile
Project Manager
(301) 827-5848

Sincerely yours,

Gregory S. Davis for

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ABLE
LABORATORIES
INC.

November 19, 2002

FEDERAL EXPRESS
Dr. Gary Buehler
Director
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

ORIG AMENDMENT
N/AA

GRATUITOUS AMENDMENT TO
ABBREVIATED NEW DRUG APPLICATION
ANDA # 76-505
METRONIDAZOLE CAPSULES
375 mg

Dear Dr. Buehler:

Pursuant to Section 505(j)(1) of the Federal Food, Drug and Cosmetic Act, ABLE LABORATORIES, INC., herewith submits a Gratuitous Amendment to our original Abbreviated New Drug Application (ANDA # 76-505) for Metronidazole Capsules, 375 mg to provide USP <671> testing for the 1250 cc HDPE bottle which was inadvertently omitted from the original submission filed on September 26, 2002.

If you should require additional information or have any questions regarding this Abbreviated New Drug Application, please do not hesitate to contact me directly by phone at (908) 754-2253, ext. 412 or by facsimile at (908) 753-9383.

We have submitted a true copy of the chemistry section to the field.

Thank you.

Sincerely,
ABLE LABORATORIES, INC.

Iva Klemick
Mrs. Iva Klemick
Director Regulatory Affairs

Volumes Submitted:
Archival -1
Field Copy -1

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6 Hollywood Court ◢ CN 1013 ◢ South Plainfield ◢ New Jersey 07080 ◢ Telephone: (908) 754-ABLE ◢ Fax: (908) 754-2476
www.ablelabs.com

ABLE
LABORATORIES
INC.

December 20, 2002

ORIG AMENDMENT

N/A

FEDERAL EXPRESS
Dr. Gary Buehler
Director
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

GRATUITOUS AMENDMENT TO
ABBREVIATED NEW DRUG APPLICATION
ANDA # 76-505
METRONIDAZOLE CAPSULES
375 mg

Dear Dr. Buehler:

Pursuant to Section 505(j)(1) of the Federal Food, Drug and Cosmetic Act, ABLE LABORATORIES, INC., herewith submits a Gratuitous Amendment to our original Abbreviated New Drug Application (ANDA # 76-505) for Metronidazole Capsules, 375 mg to provide an editorial correction of Section XVI. Stability Summary Overview, to reference capsules instead of tablets.

If you should require additional information or have any questions regarding this Abbreviated New Drug Application, please do not hesitate to contact me directly by phone at (908) 754-2253, ext. 412 or by facsimile at (908) 753-9383.

We have submitted a true copy of the chemistry section to the field.

Thank you.

Sincerely,
ABLE LABORATORIES, INC.

Iva Klemick

Mrs. Iva Klemick
Director Regulatory Affairs

Volumes Submitted:
Archival -1
Field Copy -1

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6 Hollywood Court ◂ CN 1013 ◂ South Plainfield ◂ New Jersey 07080 ◂ Telephone: (908) 754-ABLE ◂ Fax: (908) 754-2476
www.ablelabs.com

MINOR AMENDMENT

ANDA 76-505

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

MAR 4 2003

APPLICANT: Able Laboratories, Inc.

TEL: 908-754-2253 ext 412

ATTN: Iva Klemick

FAX: 908-753-9383

FROM: Wanda Pamphile

PROJECT MANAGER: 301-827-5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated September 26, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Metronidazole Capsules, 375 mg.

Reference is also made to your amendment(s) dated: November 19, and December 20, 2002.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (2 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which, will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:
Chemistry comments included. Please include in your response.

MAR 4 2003

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-505 APPLICANT: Able Laboratories, Inc.

DRUG PRODUCT: Metronidazole Capsules, 375 mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1.

2.

3.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The bioequivalence portion and the labeling portion of your submission are under review. Deficiencies, if any, will be communicated to you under separate cover.

2. The firms referenced in your application must be in compliance with cGMP at the time of approval.

3. Please provide any available drug product room temperature stability data.

4. The USP method for the drug substance and the drug product are the regulatory methods and they will prevail in the event of any dispute.

5. Please refrain from submitting testing data that are not relevant to the application, such as containers permeability test results for bottles not used for packaging Metronidazole Capsules, 375 mg.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

ABLE
LABORATORIES
INC.

March 19, 2003

FEDERAL EXPRESS
Dr. Gary Buehler
Director
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

ORIG AMENDMENT
N/AM

MINOR AMENDMENT
Metronidazole Capsules
375 mg
ANDA 76-505

Dear Dr. Buehler:

Pursuant to facsimile communication from the Agency on March 5, 2003, the firm is herewith submitting a MINOR AMENDMENT RESPONSE to our original Abbreviated New Drug Application #76-505 for Metronidazole Capsules 375 mg to provide additional chemistry information, including revised impurity limits for finished product and stability, and updated stability information.

We trust that this MINOR AMENDMENT RESPONSE to Abbreviated New Drug Application ANDA # 76-505 for Metronidazole Capsules 375 mg, meets all requirements.

If you should require additional information or have any questions regarding this MINOR AMENDMENT RESPONSE to Abbreviated New Drug Application, ANDA# 76-505, please do not hesitate to contact me directly by phone at (908) 754-2253, ext. 505 or by facsimile at (908) 753-9383.

Sincerely,

Mr. Shashikant Shah, R.Ph.
VP Quality/Regulatory Affairs

Volumes Submitted: 1

CC: District Office

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MAR 21 2003
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3/21/03

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ORIG AMENDMENT

N/AF

March 28, 2003

Dr. Gary Buehler
Director
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

LABELING AMENDMENT
FINAL APPROVAL REQUESTED

Re: Metronidazole Capsules 375 mg
ANDA 76-505

Dear Dr. Buehler:

Pursuant to facsimile communication from the Agency on March 6, 2003, the firm is herewith submitting a LABELING AMENDMENT RESPONSE to our original Abbreviated New Drug Application #76-505 for Metronidazole Capsules 375 mg to provide the requested labeling information. For ease of review, the firm has included the March 6, 2003 Labeling Amendment in reference.

Reference:

November 19, 2002	Gratuitous Amendment
December 20, 2002	Gratuitous Amendment
March 6, 2003	Labeling Amendment
March 19, 2003	Minor Amendment

1. Labeling:

There have been no changes to the container and or outsert labeling since the September 26, 2002 Original Submission, except as provided herein.

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Re: Metronidazole Capsules 375 mg
ANDA 76-505

CONTAINER LABEL

The firm has revised the container labels to include the statement "**Protect from light.**" to the storage statement.

In addition the following changes have been made:

1. The firm has changed the background color of the container label to increase the prominence of the expression of strength and product name.

2. The "DISPENSE" statement was revised to include the phrase "well-closed", based on the Reference Listed Drug.

3. The company logo was moved to the lower portion of the front panel and decreased in size.

4. The revision date was changed from 08/02 to 03/03.

For ease of review we have included a paste up side-by-side comparison of Able's last submitted container label, to Able's Final Container label which has been appended as **Exhibit #1.**

In addition, we have included an annotated * side-by-side comparison of Able's last submitted container label, to Able's Final Container label which has been appended as **Exhibit #2.**

*** [Changes are highlighted, additions are indicated by a double underline,(=) and deletions are indicated by a single strike thru (-) the word(s) or phrase(s).]**

Twelve copies of the final container labels for each packaging configuration (30s, 50s, 100s, 500s. and 1000s) have been appended as **Exhibit # 3, # 4, # 5, #6 and # 7.**

INSERT

The outsert was revised to include the following changes based on the Agency's recommendations:

1. DESCRIPTION - "Metronidazole capsules, for oral administration, contains..." [insert comma]
2. CLINICAL PHARMACOLOGY, sixth paragraph, second sentence - "...C_{max} of 8.6 (±1.6)..."
3. PRECAUTIONS, Drug interactions, second paragraph- "...phenytoin has also been reported."
4. HOW SUPPLIED- added the statement "**Protect from light.**"

In addition the firm made the following changes:

a. The degree symbol was added to the number "15".

b. The revision date was changed from 09/02 to 03/03.

For ease of review we have included a paste up side-by-side comparison of Able's last submitted outsert, to Able's Final outsert which has been appended as **Exhibit #8.**

In addition, we have included an annotated * side-by-side comparison of Able's last submitted outsert, to Able's Final outsert which has been appended as **Exhibit #9.**

***[Changes are highlighted, additions are indicated by a double underline,(=) and deletions are indicated by a single strike thru (-) the word(s) or phrase(s).]**

Twelve copies of the final outsert have been appended as **Exhibit # 10.**

2. Chemistry

There have been no changes to the Chemistry Manufacturing and Controls section of the ANDA submission since the Minor Amendment Response dated March 20, 2003 .

Re: Metronidazole Capsules 375 mg
ANDA 76-505

3. Bioequivalence

To date the firm has received no Bioequivalence comments for the titled product.

We trust this LABELING AMENDMENT RESPONSE to Abbreviated New Drug Application ANDA # 76-505 for Metronidazole Capsules 375 mg, meets all requirements.

If you should require additional information or have any questions regarding this LABELING AMENDMENT RESPONSE to Abbreviated New Drug Application, ANDA# 76-505, please do not hesitate to contact me directly by phone at (908) 754-2253, ext. 505 or by facsimile at (908) 753-9383.

Sincerely,

Mr. Shashikant Shah, R.Ph..
VP Quality/Regulatory Affairs

Volumes Submitted: 1

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May 12, 2003

NEW CORRESP
NC

FEDERAL EXPRESS
Dr. Gary Buehler
Director
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

TELEPHONE AMENDMENT
Metronidazole Capsules 375 mg
ANDA 76-505

Dear Dr. Buehler:

Pursuant to telephone communication from Ms. Wanda Pamphile, Dr. Benjamin Lim and Dr. Shing Liu of FDA and Mrs. Iva Klemick and Mr. Shashikant Shah, R.Ph. of Able Laboratories on May 12, 2003, the firm herewith commits to revise the Related Substance limits in both the Finished Product and Stability Specification Report forms for Metronidazole Capsules 375 mg, ANDA# 76-505, to reflect the revised limits of [redacted], as previously submitted for Metronidazole Extended-Release Tablets 750 mg, ANDA # 76-462.

We trust that this TELEPHONE AMENDMENT RESPONSE to Abbreviated New Drug Application ANDA # 76-505 for Metronidazole Capsules 375 mg, meets all requirements.

If you should require additional information or have any questions regarding this TELEPHONE AMENDMENT RESPONSE to Abbreviated New Drug Application, ANDA# 76-505, please do not hesitate to contact me directly by phone at (908) 754-2253, ext. 505 or by facsimile at (908) 753-9383.

Sincerely,

Iva Klemick
for Mr. Shashikant Shah, R.Ph
VP Quality and Regulatory Affairs

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May 13, 2003

FEDERAL EXPRESS

Dr. Gary Buehler
Director
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

ORIG AMENDMENT

N/ATM

TELEPHONE AMENDMENT
Metronidazole Capsules 375 mg
ANDA 76-505

Dear Dr. Buehler:

Attached please find copies of the revised finished product and stability specification report forms for Metronidazole Capsules 375 mg. referenced in my communication dated May 12, 2003.

The firm has ——— the related substance limits in each of the above referenced ANDA's, to conform to the specifications as submitted for Metronidazole Extended-Release Tablets, 750mg, ANDA # 76-462, per our commitment in our telephone conversation of May 12, 2003.

We trust that this TELEPHONE AMENDMENT RESPONSE to Abbreviated New Drug Application ANDA # 76-505 for Metronidazole Capsules 375 mg, meets all requirements.

If you should require additional information or have any questions regarding this TELEPHONE AMENDMENT RESPONSE to Abbreviated New Drug Application, ANDA# 76-505, please do not hesitate to contact me directly by phone at (908) 754-2253, ext. 505 or by facsimile at (908) 753-9383.

Sincerely,

Iva Klemick
Director, Regulatory Affairs

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May 20, 2003

Dr. Gary Buehler
Director
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

ORIG AMENDMENT
N/AF

FPL

LABELING AMENDMENT
FINAL APPROVAL REQUESTED

Re: Metronidazole Capsules 375 mg
ANDA 76-505

Dear Dr. Buehler:

Pursuant to facsimile communication from the Agency on April 30, 2003, the firm is herewith submitting a LABELING AMENDMENT RESPONSE to our original Abbreviated New Drug Application #76-505 for Metronidazole Capsules 375 mg to provide the requested labeling information. For ease of review, the firm has included the following as References:

Reference:

November 19, 2002	Gratuitous Amendment
December 20, 2002	Gratuitous Amendment
March 19, 2003	Minor Amendment Response
March 28, 2003	Labeling Amendment Response
April 30, 2003	Labeling Amendment
May 12, 2003	Telephone Amendment Response
May 13, 2003	Telephone Amendment Response

Labeling:

There have been no changes to the container and or outsert labeling since the March 28, 2003 Labeling Response.

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CONTAINER LABEL

1. **CONTAINER (Bottles of 30, 50, 100, 500 and 1000)**
   Satisfactory in final print.

The firm has not made any changes to the container label since the March 28, 2003 submission of the Final Printed Labels.

Labeling Comment # 1 has been fully addressed.

INSERT

The outsert was revised to include the following changes based on the Agency's recommendations:

2. TITLE, Warning, second sentence: "...reserved for the conditions..."
2. CLINICAL PHARMACOLOGY
   1. Fifth paragraph, last sentence: "...(± 0.4)..." [insert space after "±"]
   2. Protozoal parasites, second paragraph: "...(≥ 90%)..." [insert space after "≥"]
3. PRECAUTIONS, Geriatric Use- Due to changes in the insert labeling for the reference listed drug, (Flagyl® Capsules by Searle NDA 20-334/S-001; revised 5/5/99; approved 4/23/03), please revise the Geriatric Use subsection to read as follows:
   "No overall differences have been reported in safety and effectiveness between younger and older individuals, but greater sensitivity of some older individuals cannot be ruled out. Systemic exposure to the active metabolite, 2-hydroxymethyl metronidazole, is higher in the elderly. Metronidazole is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Although decreased renal function does not alter the single dose pharmacokinetics of metronidazole, because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it maybe useful to monitor renal function. Plasma clearance of metronidazole is decreased in patients with decreased liver function.
   Therefore, in elderly patients, monitoring of serum levels may be necessary to adjust the metronidazole dose accordingly."
4. REFERENCES, number 2: "...132(Nov): 587-591..." [insert space after "132(Nov):"]

The firm has revised the outsert according the recommendations 2A-2D.

In addition, the firm has revised the revision number from 01 to 02 and the revision date from 03/03 to 05/03.

For ease of review we have included a paste up side-by-side comparison of Able's last submitted outsert, to Able's Final outsert which has been appended as **Exhibit #1.**

In addition, we have included an annotated * side-by-side comparison of Able's last submitted outsert, to Able's Final outsert which has been appended as **Exhibit #2.**

*** [Changes are highlighted, additions are indicated by a double underline,(=) and deletions are indicated by a single strike thru (-) the word(s) or phrase(s).]**

Twelve copies of the final outsert have been appended as **Exhibit # 3.**

Chemistry

There have been no changes to the Chemistry, Manufacturing Controls Section since the May 13, 2003 Telephone Amendment.

Bioequivalence

There have been no changes to the Bioequivalence Section since the Original Submission.

APPEARS THIS WAY
ON ORIGINAL

Re: Metronidazole Capsules 375 mg
ANDA 76-505

We trust this LABELING AMENDMENT RESPONSE to Abbreviated New Drug Application ANDA # 76-505 for Metronidazole Capsules 375 mg, meets all requirements.

If you should require additional information or have any questions regarding this LABELING AMENDMENT RESPONSE to Abbreviated New Drug Application, ANDA# 76-505, please do not hesitate to contact me directly by phone at (908) 754-2253, ext. 412 or by facsimile at (908) 753-9383.

Sincerely,

Iva Klemick

Mrs. Iva Klemick
Director Regulatory Affairs

Volumes Submitted: 1

CC: District Office