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

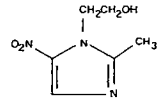
Rx Only

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).

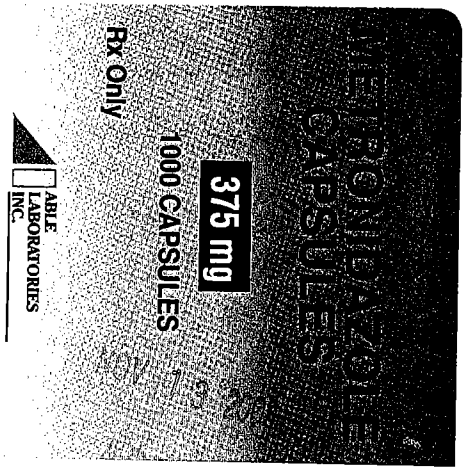
REFERENCES

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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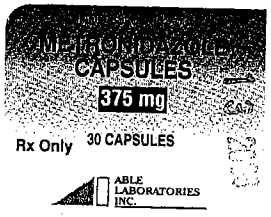
EXP. DATE:



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SOUTH PLAINFIELD, NJ 07080

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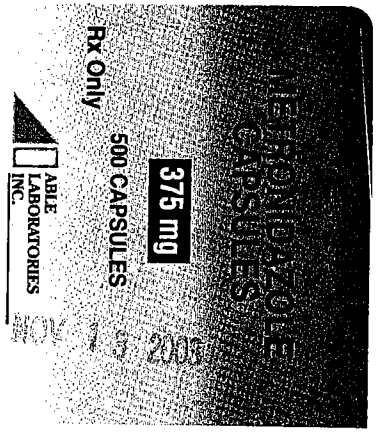
03/03

Manufacturer's Code
53265

N 3 53265-353-03 0

LOT NO.:

EXP. DATE:



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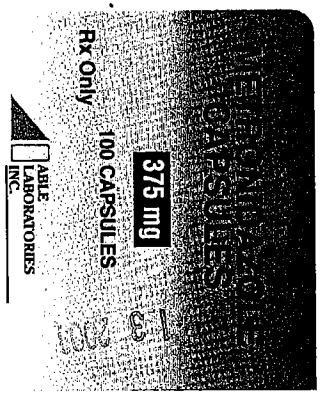
LB10281/01
03/03

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

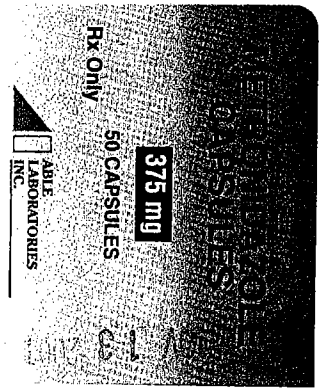
LB10280/01
03/03

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
DUP/DIVISION FILE
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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 (———).