CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 40-385

Name: Trexall Tablets (Methotrexate Tablets USP)

Sponsor: Barr Laboratories, Inc.

Approval Date: March 21, 2001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-385

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-385

APPROVAL LETTER

ANDA 40-385

MAR 21 2001

Barr Laboratories, Inc.
Attention: Christine Mundkur
2 Quaker Road
P.O. Box 2900
Pomona, NY 10970

Dear Madam:

This is in reference to your abbreviated new drug application dated July 23, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Trexall® Tablets (Methotrexate Tablets USP), 5 mg, 7.5 mg, 10 mg, and 15 mg.

Reference is also made to your amendments dated October 7, 1999, and February 15, and February 22, 2001.

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 drug product, Trexall® Tablets (Methotrexate Tablets USP), 5 mg, 7.5 mg, 10 mg, and 15 mg, can be expected to have the same therapeutic effect as equivalent doses of the listed drug product which the Agency relied upon as the basis of safety and effectiveness. 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 proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-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 FD-2253 at the time of their initial use.

Sincerely yours,

Gary Buehler 3/22/01
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 40-385
Division File
Field Copy
HFD-610/R. West
HFD-210/B. Poole
HFD-330
HFD-205

Endorsements:
HFD-625/E.Schaefer/
HFD-625/M.Smela/
HFD-617/M.Dillahunt/3/8/01
HFD-613/A.Payne/
HFD-613/J.Grace/

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F/T by: DJ 3/8/01

APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-385

APPROVED LABELING

MAR 21 2001

APPROVED

21009270101

Trexall™

(methotrexate tablets, USP)

Revised JANUARY 2001
21009270101

Rx only

WARNINGS:

METHOTREXATE SHOULD BE USED ONLY BY PHYSICIANS WHOSE KNOWLEDGE AND EXPERIENCE INCLUDE THE USE OF ANTIMETABOLITE THERAPY.

BECAUSE OF THE POSSIBILITY OF SERIOUS TOXIC REACTIONS (WHICH CAN BE FATAL):

METHOTREXATE SHOULD BE USED ONLY IN LIFE THREATENING NEOPLASTIC DISEASES, OR IN PATIENTS WITH PSORIASIS OR RHEUMATOID ARTHRITIS WITH SEVERE, RECALCITRANT, DISABLING DISEASE WHICH IS NOT ADEQUATELY RESPONSIVE TO OTHER FORMS OF THERAPY.

DEATHS HAVE BEEN REPORTED WITH THE USE OF METHOTREXATE IN THE TREATMENT OF MALIGNANCY, PSORIASIS, AND RHEUMATOID ARTHRITIS.

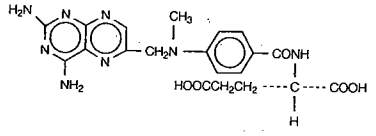
PATIENTS SHOULD BE CLOSELY MONITORED FOR BONE MARROW, LIVER, LUNG AND KIDNEY TOXICITIES. (See **PRECAUTIONS**.)

PATIENTS SHOULD BE INFORMED BY THEIR PHYSICIAN OF THE RISKS INVOLVED AND BE UNDER A PHYSICIAN'S CARE THROUGHOUT THERAPY.

1. Methotrexate has been reported to cause fetal death and/or congenital anomalies. Therefore, it is not recommended for women of childbearing potential unless there is clear medical evidence that the benefits can be expected to outweigh the considered risks. Pregnant women with psoriasis or rheumatoid arthritis should not receive methotrexate. (See **CONTRAINDICATIONS**.)
2. Methotrexate elimination is reduced in patients with impaired renal function, ascites, or pleural effusions. Such patients require especially careful monitoring for toxicity, and require dose reduction or, in some cases, discontinuation of methotrexate administration.
3. Unexpectedly severe (sometimes fatal) bone marrow suppression and gastrointestinal toxicity have been reported with concomitant administration of methotrexate (usually in high dosage) along with some nonsteroidal anti-inflammatory drugs (NSAIDs). (See **PRECAUTIONS, Drug Interactions**.)
4. Methotrexate causes hepatotoxicity, fibrosis and cirrhosis, but generally only after prolonged use. Acutely, liver enzyme elevations are frequently seen. These are usually transient and asymptomatic, and also do not appear predictive of subsequent hepatic disease. Liver biopsy after sustained use often shows histologic changes, and fibrosis and cirrhosis have been reported; these latter lesions may not be preceded by symptoms or abnormal liver function tests in the psoriasis population. For this reason, periodic liver biopsies are usually recommended for psoriatic patients who are under long-term treatment. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in the rheumatoid arthritis population. (See **PRECAUTIONS, Organ System Toxicity,** *Hepatic*.)
5. Methotrexate-induced lung disease is a potentially dangerous lesion, which may occur acutely at any time during therapy and which has been reported at doses as low as 7.5 mg/week. It is not always fully reversible. Pulmonary symptoms (especially a dry, nonproductive cough) may require interruption of treatment and careful investigation.
6. Diarrhea and ulcerative stomatitis require interruption of therapy; otherwise, hemorrhagic enteritis and death from intestinal perforation may occur.
7. Malignant lymphomas, which may regress following withdrawal of methotrexate, may occur in patients receiving low-dose methotrexate and, thus, may not require cytotoxic treatment. Discontinue methotrexate first and, if the lymphoma does not regress, appropriate treatment should be instituted.
8. Like other cytotoxic drugs, methotrexate may induce "tumor lysis syndrome" in patients with rapidly growing tumors. Appropriate supportive and pharmacologic measures may prevent or alleviate this complication.
9. Severe, occasionally fatal, skin reactions have been reported following single or multiple doses of methotrexate. Reactions have occurred within days of oral, intramuscular, intravenous, or intrathecal methotrexate administration. Recovery has been reported with discontinuation of therapy. (See **PRECAUTIONS, Organ System Toxicity,** *Skin*.)
10. Potentially fatal opportunistic infections, especially *Pneumocystis carinii* pneumonia, may occur with methotrexate therapy.
11. Methotrexate given concomitantly with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis.

DESCRIPTION:

Trexall™ (methotrexate tablets, USP) (formerly Amethopterin) is an antimetabolite used in the treatment of certain neoplastic diseases, severe psoriasis, and adult rheumatoid arthritis. Chemically methotrexate is *N*-[4[[(2,4-diamino-6-pteridinyl) methyl] methyl-amino]benzoyl]-L-glutamic acid. The structural formula is:



$C_{20}H_{22}N_8O_5$ Molecular Weight: 454.45

Trexall™ (methotrexate tablets), for oral administration, are available in 5 mg, 7.5 mg, 10 mg and 15 mg strengths in bottles of 30's, 60's and 100's.

Each 5 mg tablet contains an amount of methotrexate sodium equivalent to 5 mg of methotrexate.

Each 7.5 mg tablet contains an amount of methotrexate sodium equivalent to 7.5 mg of methotrexate.

Each 10 mg tablet contains an amount of methotrexate sodium equivalent to 10 mg of methotrexate.

Each 15 mg tablet contains an amount of methotrexate sodium equivalent to 15 mg of methotrexate.

In addition, each tablet contains the following inactive ingredients: anhydrous lactose, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, pregelatinized starch, sodium carbonate monohydrate and talc.

The 5 mg also contains: crospovidone, D&C yellow no. 10 aluminum lake, FD&C blue no. 1 aluminum lake, FD&C yellow no. 6 aluminum lake, polysorbate 80, and titanium dioxide.

The 7.5 mg also contains: crospovidone, FD&C blue no.1 aluminum lake, polysorbate 80, and titanium dioxide.

The 10 mg also contains: crospovidone, FD&C red no. 40 aluminum lake, polysorbate 80, and titanium dioxide.

The 15 mg also contains: crospovidone, FD&C blue no. 2 aluminum lake, FD&C red no. 40 aluminum lake, polysorbate 80, and titanium dioxide.

CLINICAL PHARMACOLOGY:

Methotrexate inhibits dihydrofolic acid reductase. Dihydrofolates must be reduced to tetrahydrofolates by this enzyme before they can be utilized as carriers of one-carbon groups in the synthesis of purine nucleotides and thymidylate. Therefore, methotrexate interferes with DNA synthesis, repair, and cellular replication. Actively proliferating tissues such as malignant cells, bone marrow, fetal cells, buccal and intestinal mucosa, and cells of the urinary bladder are in general more sensitive to this effect of methotrexate. When cellular proliferation in malignant tissues is greater than in most normal tissues, methotrexate may impair malignant growth without irreversible damage to normal tissues.

The mechanism of action in rheumatoid arthritis is unknown; it may affect immune function. Two reports describe *in vitro* methotrexate inhibition of DNA precursor uptake by stimulated mononuclear cells, and another describes, in animal polyarthritis partial correction by methotrexate of spleen cell hyporesponsiveness and suppressed IL 2 production. Other laboratories, however, have been unable to demonstrate similar effects. Clarification of methotrexate's effect on immune activity and its relation to rheumatoid immunopathogenesis await further studies.

In patients with rheumatoid arthritis, effects of methotrexate on articular swelling and tenderness can be seen as early as 3 to 6 weeks. Although methotrexate clearly ameliorates symptoms of inflammation (pain, swelling, stiffness), there is no evidence that it induces remission of rheumatoid arthritis nor has a beneficial effect been demonstrated on bone erosions and other radiologic changes which result in impaired joint use, functional disability, and deformity.

Most studies of methotrexate in patients with rheumatoid arthritis are relatively short term (3 to 6 months).

Limited data from long-term studies indicate that an initial clinical improvement is maintained for at least two years with continued therapy.

In psoriasis, the rate of production of epithelial cells in the skin is greatly increased over normal skin. This differential in proliferation rates is the basis for the use of methotrexate to control the psoriatic process.

Pharmacokinetics:

Absorption: In adults, oral absorption appears to be dose dependent. Peak serum levels are reached within one to two hours. At doses of 30 mg/m^2 or less, methotrexate is generally well absorbed with a mean bioavailability of about 60%. The absorption of doses greater than 80 mg/m^2 is significantly less, possibly due to a saturation effect.

In leukemic pediatric patients, oral absorption has been reported to vary widely (23% to 95%). A twenty fold difference between highest and lowest peak levels (C_{MAX}: 0.11 to 2.3 micromolar after a 20 mg/m^2 dose) has been reported. Significant interindividual variability has also been noted in time to peak concentration (T_{MAX}: 0.67 to 4 hours after a 15 mg/m^2 dose) and fraction of dose absorbed. Food has been shown to delay absorption and reduce peak concentration.

Distribution: After intravenous administration, the initial volume of distribution is approximately 0.18 L/kg (18% of body weight) and steady-state volume of distribution is approximately 0.4 to 0.8 L/kg (40 to 80% of body weight). Methotrexate competes with reduced folates for active transport across cell membranes by means of a single carrier-mediated active transport process. At serum concentrations greater than 100 micromolar, passive diffusion becomes a major pathway by which effective intracellular concentrations can be achieved. Methotrexate in serum is approximately 50% protein bound. Laboratory studies demonstrate that it may be displaced from plasma albumin by various compounds including sulfonamides, salicylates, tetracyclines, chloramphenicol, and phenytoin.

Methotrexate does not penetrate the blood-cerebrospinal fluid barrier in therapeutic amounts when given orally or parenterally. High CSF concentrations of the drug may be attained by intrathecal administration.

In dogs, synovial fluid concentrations after oral dosing were higher in inflamed than uninflamed joints. Although salicylates did not interfere with this penetration, prior prednisone treatment reduced penetration into inflamed joints to the level of normal joints.

Metabolism: After absorption, methotrexate undergoes hepatic and intracellular metabolism to polyglutamated forms which can be converted back to methotrexate by hydrolase enzymes. These polyglutamates act as inhibitors of dihydrofolate reductase and thymidylate synthetase. Small amounts of methotrexate polyglutamates may remain in tissues for extended periods. The retention and prolonged drug action of these active metabolites vary among different cells, tissues and tumors. A small amount of metabolism to 7-hydroxymethotrexate may occur at doses commonly prescribed. The aqueous solubility of 7-hydroxymethotrexate is 3 to 5 fold lower than the parent compound. Methotrexate is partially metabolized by intestinal flora after oral administration.

Half-Life: The terminal half-life reported for methotrexate is approximately three to ten hours for patients receiving treatment for psoriasis, or rheumatoid arthritis or low dose antineoplastic therapy (less than 30 mg/m^2). For patients receiving high doses of methotrexate, the terminal half-life is eight to 15 hours.

Excretion: Renal excretion is the primary route of elimination, and is dependent upon dosage and route of administration. With IV administration, 80% to 90% of the administered dose is excreted unchanged in the urine within 24 hours. There is limited biliary excretion amounting to 10% or less of the administered dose. Enterohepatic recirculation of methotrexate has been proposed.

Renal excretion occurs by glomerular filtration and active tubular secretion. Nonlinear elimination due to saturation of renal tubular reabsorption has been observed in psoriatic patients at doses between 7.5 and 30 mg. Impaired renal function, as well as concurrent use of drugs such as weak organic acids that also undergo tubular secretion, can markedly increase methotrexate serum levels. Excellent correlation has been reported between methotrexate clearance and endogenous creatinine clearance.

Methotrexate clearance rates vary widely and are generally decreased at higher doses. Delayed drug clearance has been identified as one of the major factors responsible for methotrexate toxicity. It has been postulated that the toxicity of methotrexate for normal tissues is more dependent upon the duration of exposure to the drug rather than the peak level achieved. When a patient has delayed drug elimination due to compromised renal function, a third space effusion, or other causes, methotrexate serum concentrations may remain elevated for prolonged periods.

Methotrexate has been detected in human breast milk. The highest breast milk to plasma concentration ratio reached was 0.08:1.

INDICATIONS AND USAGE:

Neoplastic Diseases:

Trexall™ (methotrexate tablets) are indicated in the treatment of gestational choriocarcinoma, chorioadenoma destruens and hydatidiform mole.

Methotrexate is used alone or in combination with other anticancer agents in the treatment of breast cancer, epidermoid cancers of the head and neck, advanced mycosis fungoides, and lung cancer, particularly squamous cell and small cell types. Methotrexate is also used in combination with other chemotherapeutic agents in the treatment of advanced stage non-Hodgkin's lymphomas.

Psoriasis:

Trexall™ (methotrexate tablets) are indicated in the symptomatic control of severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy, *but only when the diagnosis has been established, as by biopsy and/or after dermatologic consultation.* It is important to ensure that a psoriasis "flare" is not due to an undiagnosed concomitant disease affecting immune responses.

Rheumatoid Arthritis:

Trexall™ (methotrexate tablets) are indicated in the management of selected adults with severe, active, classical or definite rheumatoid arthritis (ARA criteria) who have had an insufficient therapeutic response to, or are intolerant of, an adequate trial of first-line therapy including full dose NSAIDs and usually a trial of at least one or more disease-modifying antirheumatic drugs.

Aspirin, nonsteroidal anti-inflammatory agents, and/or low dose steroids may be continued, although the possibility of increased toxicity with concomitant use of NSAIDs including salicylates has not been fully explored (see **PRECAUTIONS, Drug Interactions**). Steroids may be reduced gradually in patients who respond to methotrexate. Combined use of methotrexate with gold, penicillamine, hydroxychloroquine, sulfasalazine, or cytotoxic agents, has not been studied and may increase the incidence of adverse effects. Rest and physiotherapy as indicated should be continued.

CONTRAINDICATIONS:

Methotrexate can cause fetal death or teratogenic effects when administered to a pregnant woman. Methotrexate is contraindicated in pregnant women with psoriasis or rheumatoid arthritis and should be used in the treatment of neoplastic diseases only when the potential benefit outweighs the risk to the fetus. Women of childbearing potential should not be started on methotrexate until pregnancy is excluded and should be fully counseled on the serious risk to the fetus (see **PRECAUTIONS**) should they become pregnant while undergoing treatment. Pregnancy should be avoided if either partner is receiving methotrexate; during and for a minimum of three months after therapy for male patients, and during and for at least one ovulatory cycle after therapy for female patients. (See Boxed **WARNINGS.**)

Because of the potential for serious adverse reactions from methotrexate in breast fed infants, it is contraindicated in nursing mothers.

Patients with psoriasis or rheumatoid arthritis with alcoholism, alcoholic liver disease or other chronic liver disease should not receive methotrexate.

Patients with psoriasis or rheumatoid arthritis who have overt or laboratory evidence of immunodeficiency syndromes should not receive methotrexate.

Patients with psoriasis or rheumatoid arthritis who have preexisting blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia or significant anemia, should not receive methotrexate.

Patients with a known hypersensitivity to methotrexate should not receive the drug.

WARNINGS:

See Boxed **WARNINGS**.

PRECAUTIONS:

General:

Methotrexate has the potential for serious toxicity. (See Boxed **WARNINGS**.) Toxic effects may be related in frequency and severity to dose or frequency of administration but have been seen at all doses. Because they can occur at any time during therapy, it is necessary to follow patients on methotrexate closely. Most adverse reactions are reversible if detected early. When such reactions do occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken. If necessary, this could include the use of leucovorin calcium and/or acute, intermittent hemodialysis with a high-flux dialyzer. (See **OVERDOSAGE**.) If methotrexate therapy is reinstituted, it should be carried out with caution, with adequate consideration of further need for the drug and with increased alertness as to possible recurrence of toxicity.

The clinical pharmacology of methotrexate has not been well studied in older individuals. Due to diminished hepatic and renal function as well as decreased folate stores in this population, relatively low doses should be considered, and these patients should be closely monitored for early signs of toxicity.

Information for Patients:

Patients should be informed of the early signs and symptoms of toxicity, of the need to see their physician promptly if they occur, and the need for close follow-up, including periodic laboratory tests to monitor toxicity.

Both the physician and pharmacist should emphasize to the patient that the recommended dose is taken weekly in rheumatoid arthritis and psoriasis, and that mistaken daily use of the recommended dose has led to fatal toxicity. Prescriptions should not be written or refilled on a PRN basis.

Patients should be informed of the potential benefit and risk in the use of methotrexate. The risk of effects on reproduction should be discussed with both male and female patients taking methotrexate.

Laboratory Tests:

Patients undergoing methotrexate therapy should be closely monitored so that toxic effects are detected promptly. Baseline assessment should include a complete blood count with differential and platelet counts, hepatic enzymes, renal function tests, and a chest X-ray. During therapy of rheumatoid arthritis and psoriasis, monitoring of these parameters is recommended: hematology at least monthly, renal function and liver function every 1 to 2 months. More frequent monitoring is usually indicated during antineoplastic therapy. *During initial or changing doses,* or during periods of increased risk of elevated methotrexate blood levels (e.g., dehydration), more frequent monitoring may also be indicated.

Transient liver function test abnormalities are observed frequently after methotrexate administration and are usually not cause for modification of methotrexate therapy. Persistent liver function test abnormalities, and/or depression of serum albumin may be indicators of serious liver toxicity and require evaluation. (See **PRECAUTIONS, Organ System Toxicity,** *Hepatic.*)

A relationship between abnormal liver function tests and fibrosis or cirrhosis of the liver has not been established for patients with psoriasis. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in the rheumatoid arthritis population.

Pulmonary function tests may be useful if methotrexate-induced lung disease is suspected, especially if baseline measurements are available.

Drug Interactions:

Concomitant administration of some NSAIDs with high dose methotrexate therapy has been reported to elevate and prolong serum methotrexate levels, resulting in deaths from severe hematologic and gastrointestinal toxicity.

Caution should be used when NSAIDs or salicylates are administered concomitantly with lower doses of methotrexate. These drugs have been reported to reduce the tubular secretion of methotrexate in an animal model and may enhance its toxicity.

Despite the potential interactions, studies of methotrexate in patients with rheumatoid arthritis have usually included concurrent use of constant dosage regimens of NSAIDs, without apparent problems. It should be appreciated, however, that the doses used in rheumatoid arthritis (7.5 to 15 mg/week) are somewhat lower than those used in psoriasis and that larger doses could lead to unexpected toxicity.

Methotrexate is partially bound to serum albumin, and toxicity may be increased because of displacement by certain drugs, such as salicylates, phenylbutazone, phenytoin, and sulfonamides. Renal tubular transport is also diminished by probenecid; use of methotrexate with this drug should be carefully monitored.

Oral antibiotics such as tetracycline, chloramphenicol, and nonabsorbable broad spectrum antibiotics, may decrease intestinal absorption of methotrexate or interfere with the enterohepatic circulation by inhibiting bowel flora and suppressing metabolism of the drug by bacteria.

Penicillins may reduce the renal clearance of methotrexate; increased serum concentrations of methotrexate with concomitant hematologic and gastrointestinal toxicity have been observed with high and low dose methotrexate. Use of methotrexate with penicillins should be carefully monitored.

The potential for increased hepatotoxicity when methotrexate is administered with other hepatotoxic agents has not been evaluated. However, hepatotoxicity has been reported in such cases. Therefore, patients receiving concomitant therapy with methotrexate and other potential hepatotoxins (e.g., azathioprine, retinoids, sulfasalazine) should be closely monitored for possible increased risk of hepatotoxicity.

Methotrexate may decrease the clearance of theophylline; theophylline levels should be monitored when used concurrently with methotrexate.

Vitamin preparations containing folic acid or its derivatives may decrease responses to systemically administered methotrexate. Preliminary animal and human studies have shown that small quantities of intravenously administered leucovorin enter the CSF primarily as 5-methyltetrahydrofolate and, in humans, remain 1-3 orders of magnitude lower than the usual methotrexate concentrations following intrathecal administration. However, high doses of leucovorin may reduce the efficacy of intrathecally administered methotrexate.

Folate deficiency states may increase methotrexate toxicity.

Trimethoprim/sulfamethoxazole has been reported rarely to increase bone marrow suppression in patients receiving methotrexate, probably by an additive antifolate effect.

Carcinogenesis, Mutagenesis, and Impairment of Fertility:

No controlled human data exist regarding the risk of neoplasia with methotrexate. Methotrexate has been evaluated in a number of animal studies for carcinogenic potential with inconclusive results. Although there is evidence that methotrexate causes chromosomal damage to animal somatic cells and human bone marrow cells, the clinical significance remains uncertain. Non-Hodgkin's lymphoma and other tumors have been reported in patients receiving low-dose oral methotrexate. However, there have been instances of malignant lymphoma arising during treatment with low-dose oral methotrexate, which have regressed completely following withdrawal of methotrexate, without requiring active anti-lymphoma treatment. Benefits should be weighed against the potential risks before using methotrexate alone or in combination with other drugs, especially in pediatric patients or young adults. Methotrexate causes embryotoxicity, abortion, and fetal defects in humans. It has also been reported to cause impairment of fertility, oligospermia and menstrual dysfunction in humans, during and for a short period after cessation of therapy.

Pregnancy:

Psoriasis and rheumatoid arthritis: Methotrexate is in Pregnancy Category X. See **CONTRAINDICATIONS**.

Nursing Mothers:

See **CONTRAINDICATIONS**.

Pediatric Use:

Safety and effectiveness in pediatric patients have not been established, other than in cancer chemotherapy.

Organ System Toxicity:

Gastrointestinal: If vomiting, diarrhea, or stomatitis occur, which may result in dehydration, methotrexate should be discontinued until recovery occurs. Methotrexate should be used with extreme caution in the presence of peptic ulcer disease or ulcerative colitis.

Hematologic: Methotrexate can suppress hematopoiesis and cause anemia, leukopenia, and/or thrombocytopenia. In patients with malignancy and preexisting hematopoietic impairment, the drug should be used with caution, if at all. In controlled clinical trials in rheumatoid arthritis (n=128), leukopenia (WBC <3000/mm^3) was seen in 2 patients, thrombocytopenia (platelets <100,000/mm^3) in 6 patients, and pancytopenia in 2 patients.

In psoriasis and rheumatoid arthritis, methotrexate should be stopped immediately if there is a significant drop in blood counts. In the treatment of neoplastic diseases, methotrexate should be continued only if the potential benefit warrants the risk of severe myelosuppression. Patients with profound granulocytopenia and fever should be evaluated immediately and usually require parenteral broad-spectrum antibiotic therapy.

Hepatic: Methotrexate has the potential for acute (elevated transaminases) and chronic (fibrosis and cirrhosis) hepatotoxicity. Chronic toxicity is potentially fatal; it generally has occurred after prolonged use (generally two years or more) and after a total dose of at least 1.5 grams. In studies in psoriatic patients, hepatotoxicity appeared to be a function of total cumulative dose and appeared to be enhanced by alcoholism, obesity, diabetes and advanced age. An accurate incidence rate has not been determined; the rate of progression and reversibility of lesions is not known. Special caution is indicated in the presence of preexisting liver damage or impaired hepatic function.

(Over)

In psoriasis, liver function tests, including serum albumin, should be performed periodically prior to dosing but are often normal in the face of developing fibrosis or cirrhosis. These lesions may be detectable only by biopsy. The usual recommendation is to obtain a liver biopsy at 1) pretherapy or shortly after initiation of therapy (2-4 months), 2) a total cumulative dose of 1.5 grams, and 3) after each additional 1.0 to 1.5 grams. Moderate fibrosis or any cirrhosis normally leads to discontinuation of the drug; mild fibrosis normally suggests a repeat biopsy in 6 months. Milder histologic findings such as fatty change and low grade portal inflammation are relatively common pretherapy. Although these mild changes are usually not a reason to avoid or discontinue methotrexate therapy, the drug should be used with caution.

In rheumatoid arthritis, age at first use of methotrexate and duration of therapy have been reported as risk factors for hepatotoxicity; other risk factors, similar to those observed in psoriasis, may be present in rheumatoid arthritis but have not been confirmed to date. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in this population. There is a combined reported experience in 217 rheumatoid arthritis patients with liver biopsies both before and during treatment (after a cumulative dose of at least 1.5 g) and in 714 patients with a biopsy only during treatment. There are 64 (7%) cases of fibrosis and 1 (0.1%) cases of cirrhosis. Of the 64 cases of fibrosis, 60 were deemed mild. The reticulin stain is more sensitive for early fibrosis and its use may increase these figures. It is unknown whether even longer use will increase these risks.

Liver function tests should be performed at baseline and at 4-8 week intervals in patients receiving methotrexate for rheumatoid arthritis. Pretreatment liver biopsy should be performed for patients with a history of excessive alcohol consumption, persistently abnormal baseline liver function test values or chronic hepatitis B or C infection. During therapy, liver biopsy should be performed if there are persistent liver function test abnormalities or there is a decrease in serum albumin below the normal range (in the setting of well controlled rheumatoid arthritis).

If the results of a liver biopsy show mild changes (Roenigk grades I, II, IIIa), methotrexate may be continued and the patient monitored as per recommendations listed above. Methotrexate should be discontinued in any patient who displays persistently abnormal liver function tests and refuses liver biopsy or in any patient whose liver biopsy shows moderate to severe changes (Roenigk grade IIIb or IV).[2]

Infection or Immunologic States: Methotrexate should be used with extreme caution in the presence of active infection, and is usually contraindicated in patients with overt or laboratory evidence of immunodeficiency syndromes. Immunization may be ineffective when given during methotrexate therapy. Immunization with live virus vaccines is generally not recommended. There have been reports of disseminated vaccinia infections after smallpox immunization in patients receiving methotrexate therapy. Hypogammaglobulinemia has been reported rarely.

Potentially fatal opportunistic infections, especially *Pneumocystis carinii* pneumonia, may occur with methotrexate therapy. When a patient presents with pulmonary symptoms, the possibility of *Pneumocystis carinii* pneumonia should be considered.

Neurologic: There have been reports of leukoencephalopathy following intravenous administration of methotrexate to patients who have had craniospinal irradiation. Serious neurotoxicity, frequently manifested as generalized or local seizures, has been reported with unexpectedly increased frequency among pediatric patients with acute lymphoblastic leukemia who were treated with intermediate-dose intravenous methotrexate (1 gm/m^2). Symptomatic patients were commonly noted to have leukoencephalopathy and/or microangiopathic calcifications on diagnostic imaging studies. Chronic leukoencephalopathy has also been reported in patients who received repeated doses of high-dose methotrexate with leucovorin rescue even without cranial irradiation. Discontinuation of methotrexate does not always result in complete recovery.

A transient acute neurologic syndrome has been observed in patients treated with high dosage regimens. Manifestations of this stroke-like encephalopathy may include confusion, hemiparesis, seizures and coma. The exact cause is unknown.

Pulmonary: Pulmonary symptoms (especially a dry nonproductive cough) or a nonspecific pneumonitis occurring during methotrexate therapy may be indicative of a potentially dangerous lesion and require interruption of treatment and careful investigation. Although clinically variable, the typical patient with methotrexate induced lung disease presents with fever, cough, dyspnea, hypoxemia, and an infiltrate on chest X-ray; infection needs to be excluded. This lesion can occur at all dosages.

Renal: High doses of methotrexate used in the treatment of osteosarcoma may cause renal damage leading to acute renal failure. Nephrotoxicity is due primarily to the precipitation of methotrexate and 7-hydroxymethotrexate in the renal tubules. Close attention to renal function including adequate hydration, urine alkalinization and measurement of serum methotrexate and creatinine levels are essential for safe administration.

Skin: Severe, occasionally fatal, dermatologic reactions, including toxic epidermal necrolysis, Stevens-Johnson Syndrome, exfoliative dermatitis, skin necrosis, and erythema multiforme, have been reported in children and adults, within days of oral, intramuscular, intravenous, or intrathecal methotrexate administration. Reactions were noted after single or multiple, low intermediate or high doses of methotrexate in patients with neoplastic and non-neoplastic diseases.

Other Precautions: Methotrexate should be used with extreme caution in the presence of debility.

Methotrexate exits slowly from third-space compartments (e.g., pleural effusions or ascites). This results in a prolonged terminal plasma half-life and unexpected toxicity. In patients with significant third-space accumulations, it is advisable to evacuate the fluid before treatment and to monitor plasma methotrexate levels.

Lesions of psoriasis may be aggravated by concomitant exposure to ultraviolet radiation. Radiation dermatitis and sunburn may be "recalled" by the use of methotrexate.

ADVERSE REACTIONS:

IN GENERAL, THE INCIDENCE AND SEVERITY OF ACUTE SIDE EFFECTS ARE RELATED TO DOSE AND FREQUENCY OF ADMINISTRATION. THE MOST SERIOUS REACTIONS ARE DISCUSSED ABOVE UNDER ORGAN SYSTEM TOXICITY IN THE PRECAUTION SECTION. THAT SECTION SHOULD ALSO BE CONSULTED WHEN LOOKING FOR INFORMATION ABOUT ADVERSE REACTIONS WITH METHOTREXATE.

The most frequently reported adverse reactions include ulcerative stomatitis, leukopenia, nausea, and abdominal distress. Other frequently reported adverse effects are malaise, undue fatigue, chills and fever, dizziness and decreased resistance to infection.

Other adverse reactions that have been reported with methotrexate are listed below by organ system. In the oncology setting, concomitant treatment and the underlying disease make specific attribution of a reaction to methotrexate difficult.

Alimentary System: Gingivitis, pharyngitis, stomatitis, anorexia, nausea, vomiting, diarrhea, hematemesis, melena, gastrointestinal ulceration and bleeding, enteritis, pancreatitis.

Cardiovascular: Pericarditis, pericardial effusion, hypotension, and thromboembolic events (including arterial thrombosis, cerebral thrombosis, deep vein thrombosis, retinal vein thrombosis, thrombophlebitis, and pulmonary embolus).

Central Nervous System: Headaches, drowsiness, blurred vision. Aphasia, hemiparesis, paresis and convulsions have also occurred following administration of methotrexate. Following low doses, there have been occasional reports of transient subtle cognitive dysfunction, mood alteration, unusual cranial sensation, leukoencephalopathy, or encephalopathy.

Infection: There have been case reports of sometimes fatal opportunistic infections in patients receiving methotrexate therapy for neoplastic and non-neoplastic diseases. *Pneumocystis carinii* pneumonia was the most common infection. Other reported infections included nocardiosis, histoplasmosis, cryptococcosis, *Herpes zoster, H. simplex* hepatitis, and disseminated *H. simplex*.

Ophthalmic: Conjunctivitis, serious visual changes of unknown etiology.

Pulmonary System: Interstitial pneumonitis deaths have been reported, and chronic interstitial obstructive pulmonary disease has occasionally occurred.

Skin: Erythematous rashes, pruritus, urticaria, photosensitivity, pigmentary changes, alopecia, ecchymosis, telangiectasia, acne, furunculosis, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson Syndrome, skin necrosis, and exfoliative dermatitis.

Urogenital System: Severe nephropathy or renal failure, azotemia, cystitis, hematuria; defective oogenesis or spermatogenesis, transient oligospermia, menstrual dysfunction, vaginal discharge, and gynecomastia; infertility, abortion, fetal defects.

Other rarer reactions related to or attributed to the use of methotrexate such as nodulosis, vasculitis, arthralgia/myalgia, loss of libido/impotence, diabetes, osteoporosis, sudden death, reversible lymphomas, tumor lysis syndrome, soft tissue necrosis and osteonecrosis. Anaphylactoid reactions have been reported.

Adverse Reactions in Double-Blind Rheumatoid Arthritis Studies:

The approximate incidences of methotrexate-attributed (i.e., placebo rate subtracted) adverse reactions in 12 to 18 week double-blind studies of patients (n=128) with rheumatoid arthritis treated with low-dose oral (7.5 to 15 mg/week) pulse methotrexate, are listed below. Virtually all of these patients were on concomitant nonsteroidal anti-inflammatory drugs and some were also taking low dosages of corticosteroids.

Incidence greater than 10%: Elevated liver function tests 15%, nausea/vomiting 10%.

Incidence 3% to 10%: Stomatitis, thrombocytopenia, (platelet count less than 100,000/mm^3).

Incidence 1% to 3%: Rash/pruritus/dermatitis, diarrhea, alopecia, leukopenia (WBC less than 3000/mm^3), pancytopenia, dizziness.

No pulmonary toxicity was seen in these two trials. Thus, the incidence is probably less than 2.5% (95% C.L.). Hepatic histology was not examined in these short-term studies (see **PRECAUTIONS**).

Other less common reactions included decreased hematocrit, headache, upper respiratory infection, anorexia, arthralgias, chest pain, coughing, dysuria, eye discomfort, epistaxis, fever, infection, sweating, tinnitus, and vaginal discharge.

Adverse Reactions in Psoriasis:

There are no recent placebo-controlled trials in patients with psoriasis. There are two literature reports (Roenigk, 1969 and Nyfors, 1978) describing large series (n=204, 248) of psoriasis patients treated with methotrexate. Dosages ranged up to 25 mg per week and treatment was administered for up to four years. With the exception of alopecia, photosensitivity, and "burning of skin lesions" (each 3% to 10%), the adverse reaction rates in these reports were very similar to those in the rheumatoid arthritis studies.

Rarely, painful plaque erosions may appear (Pearce, HP and Wilson, BB: *Am Acad Dermatol* 35:835-838, 1996).

OVERDOSAGE:

Leucovorin is indicated to diminish the toxicity and counteract the effect of inadvertently administered overdosages of methotrexate. Leucovorin administration should begin as promptly as possible. As the time interval between methotrexate administration and leucovorin initiation increases, the effectiveness of leucovorin in counteracting toxicity decreases. Monitoring of the serum methotrexate concentration is essential in determining the optimal dose and duration of treatment with leucovorin.

In cases of massive overdosage, hydration and urinary alkalinization may be necessary to prevent the precipitation of methotrexate and/or its metabolites in the renal tubules. Generally speaking, neither hemodialysis nor peritoneal dialysis have been shown to improve methotrexate elimination. However, effective clearance of methotrexate has been reported with acute, intermittent hemodialysis using a high-flux dialyzer. (Wall, SM et al: *AM J Kidney Dis* 28(6):846-854, 1996).

DOSAGE AND ADMINISTRATION:

Neoplastic Diseases:

Oral administration in tablet form is often preferred when low doses are being administered since absorption is rapid and effective serum levels are obtained.

Choriocarcinoma and similar trophoblastic diseases: Methotrexate is administered orally or intramuscularly in doses of 15 to 30 mg daily for a five-day course. Such courses are usually repeated for 3 to 5 times as required, with rest periods of one or more weeks interposed between courses, until any manifesting toxic symptoms subside. The effectiveness of therapy is ordinarily evaluated by 24-hour quantitative analysis of urinary chorionic gonadatropin (hCG), which should return to normal or less than 50 IU/24 hr usually after the third or fourth course and usually be followed by a complete resolution of measurable lesions in 4 to 6 weeks. One to two courses of methotrexate after normalization of hCG is usually recommended. Before each course of the drug careful clinical assessment is essential. Cyclic combination therapy of methotrexate with other antitumor drugs has been reported as being useful.

Since hydatidiform mole may precede choriocarcinoma, prophylactic chemotherapy with methotrexate has been recommended.

Chorioadenoma destruens is considered to be an invasive form of hydatidiform mole. Methotrexate is administered in these disease states in doses similar to those recommended for choriocarcinoma.

Leukemia: Acute lymphoblastic leukemia in pediatric patients is the most responsive to present day chemotherapy. In young adults and older patients, clinical remission is more difficult to obtain and early relapse is more common.

Methotrexate alone or in combination with steroids was used initially for induction of remission in acute lymphoblastic leukemias. More recently corticosteroid therapy, in combination with other antileukemic drugs or in cyclic combinations with methotrexate included, has appeared to produce rapid and effective remissions. When used for induction, methotrexate in doses of 3.3 mg/m^2 in combination with 60 mg/m^2 of prednisone, given daily, produced remissions in 50% of patients treated, usually within a period of 4 to 6 weeks. Methotrexate in combination with other agents appears to be the drug of choice for securing maintenance of drug-induced remissions. When remission is achieved and supportive care has produced general clinical improvement, maintenance therapy is initiated, as follows: Methotrexate is administered 2 times weekly either by mouth or intramuscularly in total weekly doses of 30 mg/m^2. It has also been given in doses of 2.5 mg/kg intravenously every 14 days. If and when relapse does occur, reinduction of remission can again usually be obtained by repeating the initial induction regimen.

A variety of combination chemotherapy regimens have been used for both induction and maintenance therapy in acute lymphoblastic leukemia. The physician should be familiar with the new advances in antileukemic therapy.

Lymphomas: In Burkitt's tumor, Stages I-II, methotrexate has produced prolonged remissions in some cases. Recommended dosage is 10 to 25 mg/day orally for 4 to 8 days. In Stage III, methotrexate is commonly given concomitantly with other antitumor agents. Treatment in all stages usually consists of several courses of the drug interposed with 7 to 10 day rest periods. Lymphosarcomas in Stage III may respond to combined drug therapy with methotrexate given in doses of 0.625 to 2.5 mg/kg daily.

Mycosis fungoides: Therapy with methotrexate appears to produce clinical remissions in one-half of the cases treated. Dosage is usually 2.5 to 10 mg daily by mouth for weeks or months. Dose levels of drug and adjustment of dose regimen by reduction or cessation of drug are guided by patient response and hematologic monitoring. Methotrexate has also been given intramuscularly in doses of 50 mg once weekly or 25 mg, 2 times weekly.

Psoriasis and Rheumatoid Arthritis:

The patient should be fully informed of the risks involved and should be under constant supervision of the physician (see **Information for Patients** under **PRECAUTIONS**). Assessment of hematologic, hepatic, renal, and pulmonary function should be made by history, physical examination, and laboratory tests before beginning, periodically during, and before reinstituting methotrexate therapy (see **PRECAUTIONS**). Appropriate steps should be taken to avoid conception during methotrexate therapy (see **PRECAUTIONS** and **CONTRAINDICATIONS**).

Weekly therapy may be instituted to provide doses over a range of 5 mg to 15 mg administered as a single weekly dose. All schedules should be continually tailored to the individual patient. An initial test dose may be given prior to the regular dosing schedule to detect any extreme sensitivity to adverse effects (see **ADVERSE REACTIONS**). Maximal myelosuppression usually occurs in seven to ten days.

Psoriasis: Recommended Starting Dose Schedules:

1. Weekly single oral, IM or IV dosage schedule: 10 to 25 mg per week until adequate response is achieved.
2. Divided oral dose schedule: 2.5 mg at 12-hour intervals for three doses.

Dosages in each schedule may be gradually adjusted to achieve optimal clinical response; 30 mg/week should not ordinarily be exceeded.

Once optimal clinical response has been achieved, each dosage schedule should be reduced to the lowest possible amount of drug and to the longest possible rest period. The use of methotrexate may permit the return to conventional topical therapy, which should be encouraged.

Rheumatoid Arthritis: Recommended Starting Dosage Schedules:

1. Single oral doses of 7.5 mg once weekly.
2. Divided oral dosages of 2.5 mg at 12-hour intervals for 3 doses given as a course once weekly.

Dosages in each schedule may be adjusted gradually to achieve an optimal response, but not ordinarily to exceed a total weekly dose of 20 mg. Limited experience shows a significant increase in the incidence and severity of serious toxic reactions, especially bone marrow suppression, at doses greater than 20 mg/wk.

Once response has been achieved, each schedule should be reduced, if possible, to the lowest possible effective dose.

Therapeutic response usually begins within 3 to 6 weeks and the patient may continue to improve for another 12 weeks or more.

The optimal duration of therapy is unknown. Limited data available from long-term studies indicate that the initial clinical improvement is maintained for at least two years with continued therapy. When methotrexate is discontinued, the arthritis usually worsens within 3 to 6 weeks.

HANDLING AND DISPOSAL:

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-8] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED:

Trexall™ (methotrexate tablets, USP) are available as:

5 mg: Green, oval-shaped, film-coated, scored, biconvex tablet. Debossed with **b** on one side and **927/5** on the other side. Each 5 mg tablet contains an amount of methotrexate sodium equivalent to 5 mg of methotrexate.

Available in bottles of:

30 NDC 0555-0927-01
60 NDC 0555-0927-09
100 NDC 0555-0927-02

7.5 mg: Blue, oval-shaped, film-coated, scored, biconvex tablet. Debossed with **b** on one side and **928/7-1/2** on the other side. Each 7.5 mg tablet contains an amount of methotrexate sodium equivalent to 7.5 mg of methotrexate.

Available in bottles of:

30 NDC 0555-0928-01
60 NDC 0555-0928-09
100 NDC 0555-0928-02

10 mg: Pink, oval-shaped, film-coated, scored, biconvex tablet. Debossed with **b** on one side and **929/10** on the other side. Each 10 mg tablet contains an amount of methotrexate sodium equivalent to 10 mg of methotrexate.

Available in bottles of:

30 NDC 0555-0929-01
60 NDC 0555-0929-09
100 NDC 0555-0929-02

15 mg: Purple, oval-shaped, film-coated, scored, biconvex tablet. Debossed with **b** on one side and **945/15** on the other side. Each 15 mg tablet contains an amount of methotrexate sodium equivalent to 15 mg of methotrexate.

Available in bottles of:

30 NDC 0555-0945-01
60 NDC 0555-0945-09
100 NDC 0555-0945-02

Dispense with a child-resistant closure in a well-closed container as defined in the USP.

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

Protect from light.

REFERENCES:

1. Controlling occupational exposure to hazardous drugs (OSHA Work-Practice Guidelines). *Am J Health Syst Pharm* 1996; 53:1669-1685.
2. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents, US Government Printing Office, Washington, DC 20402.
3. AMA Council Report. Guidelines for Handling Parenteral Antineoplastics. *JAMA*, 1985; 253(11):1590-1592.
4. National Study Commission on Cytotoxic Exposure - Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, Sc D, Chairman, National Study Commisssion on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston Massachusetts 02115.
5. Clinical Oncological Society of Australia: Guidelines and recommendations for safe handling of antineoplastic agents. *Med J Australia* 1983; 1:426-428.
6. Jones RB, et al. Safe handling of chemotherapeutic agents: A report from the Mount Sinai Medical Center. Ca - *A Cancer Journal for Clinicians* Sept/Oct 1983; 258-263.
7. American Society of Hospital Pharmacists technical assistance bulletin on handling cytotoxic and hazardous drugs. *Am J Hosp Pharm* 1990; 47:1033-1049.
8. OSHA Work-Practice Guidelines for Personnel Dealing with Cytotoxic (Antineoplastic) Drugs. *Am J Hosp Pharm*, 1986; 43:1193-1204.

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Revised JANUARY 2001
BR-927, 928, 929, 945

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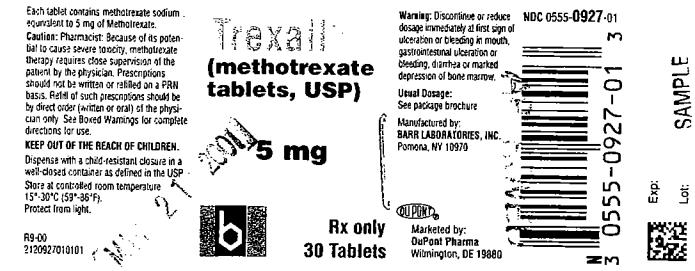

Each tablet contains methotrexate sodium equivalent to 5 mg of Methotrexate.
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KEEP OUT OF THE REACH OF CHILDREN.
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Store at controlled room temperature 15°-30°C (59°-86°F).
Protect from light.
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Trexall™
(methotrexate tablets, USP)
5 mg
Rx only
30 Tablets

Warning: Discontinue or reduce dosage immediately at first sign of ulceration or bleeding in mouth, gastrointestinal ulceration or bleeding, diarrhea or marked depression of bone marrow.
Usual Dosage:
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Manufactured by:
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Wilmington, DE 19880

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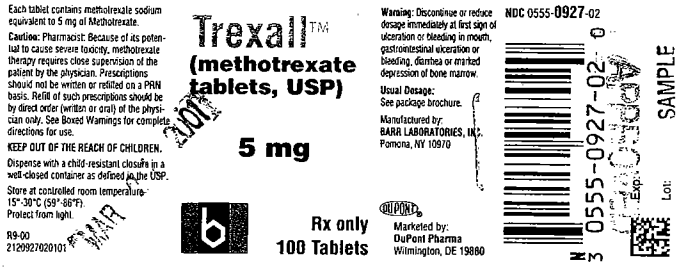

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Trexall™
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Rx only
100 Tablets

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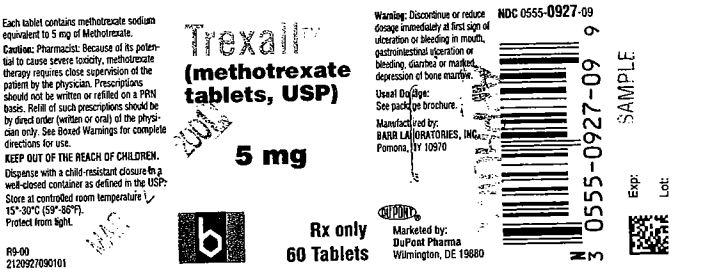

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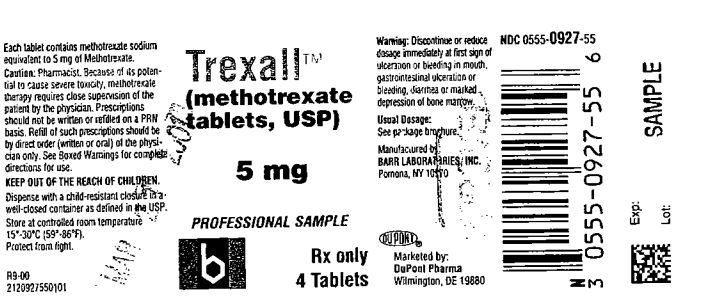

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Trexall™
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5 mg
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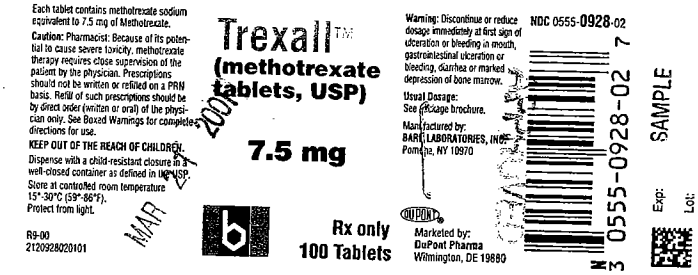
Each tablet contains methotrexate sodium equivalent to 7.5 mg of Methotrexate.
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7.5 mg
Rx only
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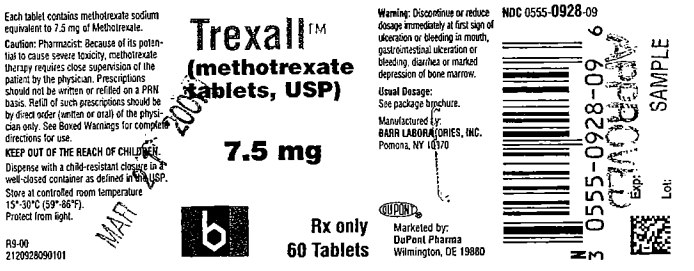
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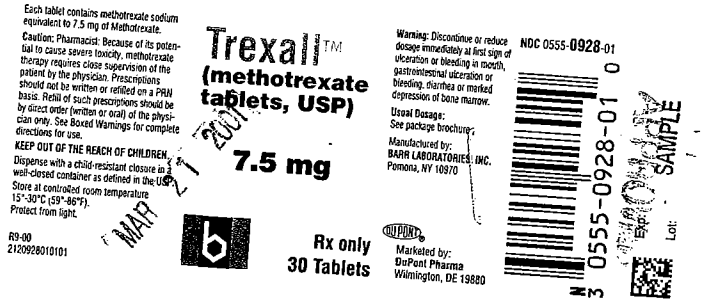
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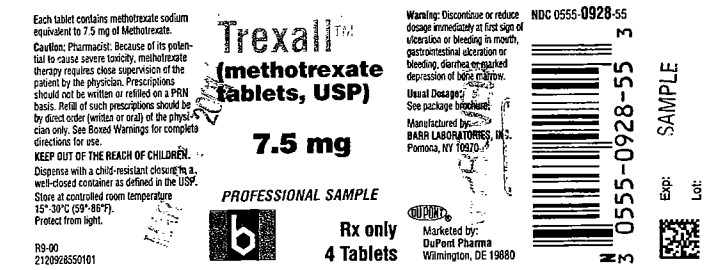
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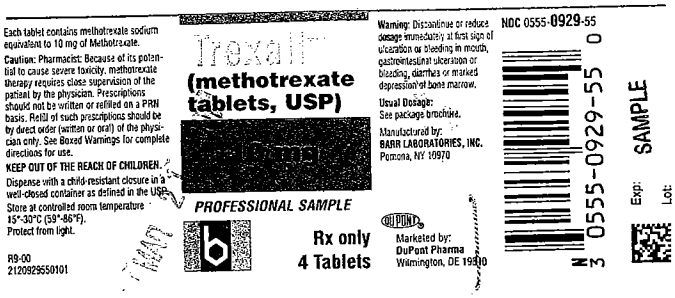
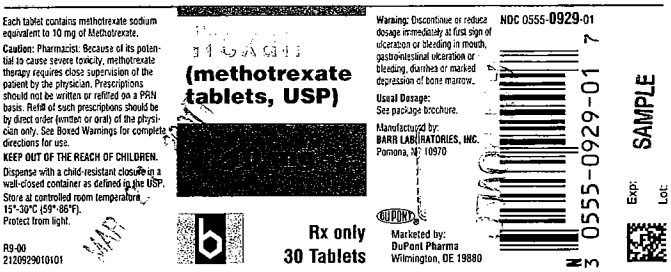
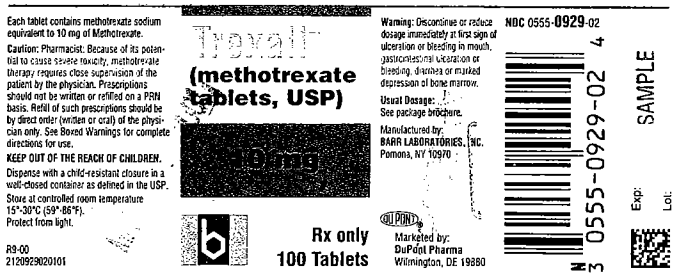
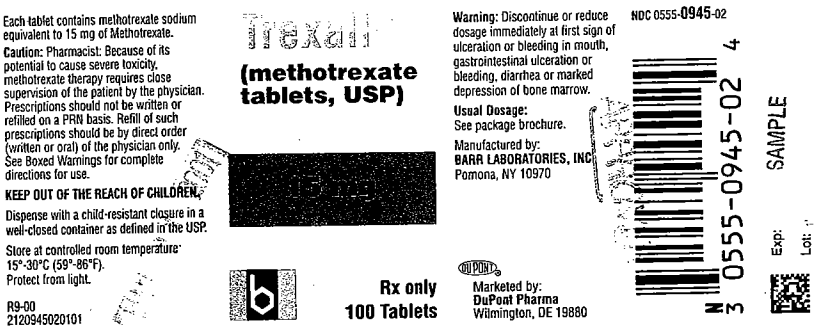

Each tablet contains methotrexate sodium equivalent to 10 mg of Methotrexate.
Caution: Pharmacist: Because of its potential to cause severe toxicity, methotrexate therapy requires close supervision of the patient by the physician. Prescriptions should not be written or refilled on a PRN basis. Refill of such prescriptions should be by direct order (written or oral) of the physician only. See Boxed Warnings for complete directions for use.
KEEP OUT OF THE REACH OF CHILDREN.
Dispense with a child-resistant closure in a well-closed container as defined in the USP.
Store at controlled room temperature 15°-30°C (59°-86°F).
Protect from light.
R9-00
2120929550101
Trexall™
(methotrexate tablets, USP)
PROFESSIONAL SAMPLE
Rx only
4 Tablets
Warning: Discontinue or reduce dosage immediately at first sign of ulceration or bleeding in mouth, gastrointestinal ulceration or bleeding, diarrhea or marked depression of bone marrow.
Usual Dosage:
See package brochure.
Manufactured by:
BARR LABORATORIES, INC.
Pomona, NY 10970
DUPONT
Marketed by:
DuPont Pharma
Wilmington, DE 19880
NDC 0555-0929-55
3 0555-0929-55 0
SAMPLE
Exp:
Lot:

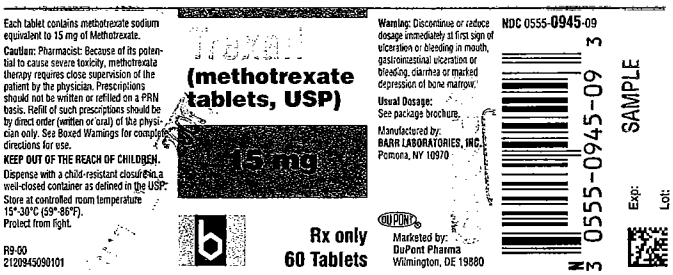

Each tablet contains methotrexate sodium equivalent to 10 mg of Methotrexate.
Caution: Pharmacist: Because of its potential to cause severe toxicity, methotrexate therapy requires close supervision of the patient by the physician. Prescriptions should not be written or refilled on a PRN basis. Refill of such prescriptions should be by direct order (written or oral) of the physician only. See Boxed Warnings for complete directions for use.
KEEP OUT OF THE REACH OF CHILDREN.
Dispense with a child-resistant closure in a well-closed container as defined in the USP.
Store at controlled room temperature 15°-30°C (59°-86°F).
Protect from light.
R9-00
2120929010101
(methotrexate tablets, USP)
Rx only
30 Tablets
Warning: Discontinue or reduce dosage immediately at first sign of ulceration or bleeding in mouth, gastrointestinal ulceration or bleeding, diarrhea or marked depression of bone marrow.
Usual Dosage:
See package brochure.
Manufactured by:
BARR LABORATORIES, INC.
Pomona, NY 10970
DUPONT
Marketed by:
DuPont Pharma
Wilmington, DE 19880
NDC 0555-0929-01
3 0555-0929-01 7
SAMPLE
Exp:
Lot:

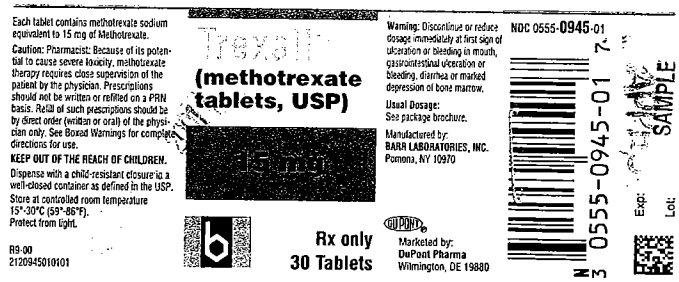

Each tablet contains methotrexate sodium equivalent to 10 mg of Methotrexate.
Caution: Pharmacist: Because of its potential to cause severe toxicity, methotrexate therapy requires close supervision of the patient by the physician. Prescriptions should not be written or refilled on a PRN basis. Refill of such prescriptions should be by direct order (written or oral) of the physician only. See Boxed Warnings for complete directions for use.
KEEP OUT OF THE REACH OF CHILDREN.
Dispense with a child-resistant closure in a well-closed container as defined in the USP.
Store at controlled room temperature 15°-30°C (59°-86°F).
Protect from light.
R9-00
2120929090101
Trexall™
(methotrexate tablets, USP)
Rx only
60 Tablets
Warning: Discontinue or reduce dosage immediately at first sign of ulceration or bleeding in mouth, gastrointestinal ulceration or bleeding, diarrhea or marked depression of bone marrow.
Usual Dosage:
See package brochure.
Manufactured by:
BARR LABORATORIES, INC.
Pomona, NY 10970
DUPONT
Marketed by:
DuPont Pharma
Wilmington, DE 19880
NDC 0555-0929-09
3 0555-0929-09 3
SAMPLE
Exp:
Lot:

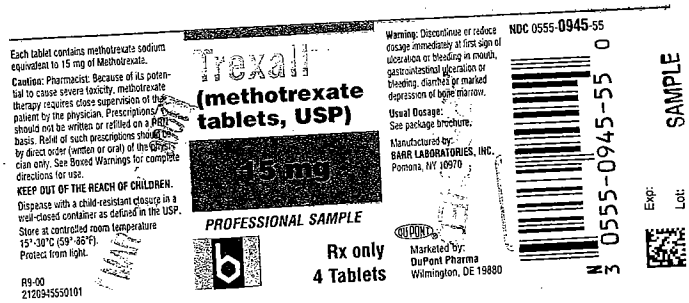

Each tablet contains methotrexate sodium equivalent to 10 mg of Methotrexate.
Caution: Pharmacist: Because of its potential to cause severe toxicity, methotrexate therapy requires close supervision of the patient by the physician. Prescriptions should not be written or refilled on a PRN basis. Refill of such prescriptions should be by direct order (written or oral) of the physician only. See Boxed Warnings for complete directions for use.
KEEP OUT OF THE REACH OF CHILDREN.
Dispense with a child-resistant closure in a well-closed container as defined in the USP.
Store at controlled room temperature 15°-30°C (59°-86°F).
Protect from light.
R9-00
2120929020101
Trexall™
(methotrexate tablets, USP)
Rx only
100 Tablets
Warning: Discontinue or reduce dosage immediately at first sign of ulceration or bleeding in mouth, gastrointestinal ulceration or bleeding, diarrhea or marked depression of bone marrow.
Usual Dosage:
See package brochure.
Manufactured by:
BARR LABORATORIES, INC.
Pomona, NY 10970
DUPONT
Marketed by:
DuPont Pharma
Wilmington, DE 19880
NDC 0555-0929-02
3 0555-0929-02 4
SAMPLE
Exp:
Lot:

40-385

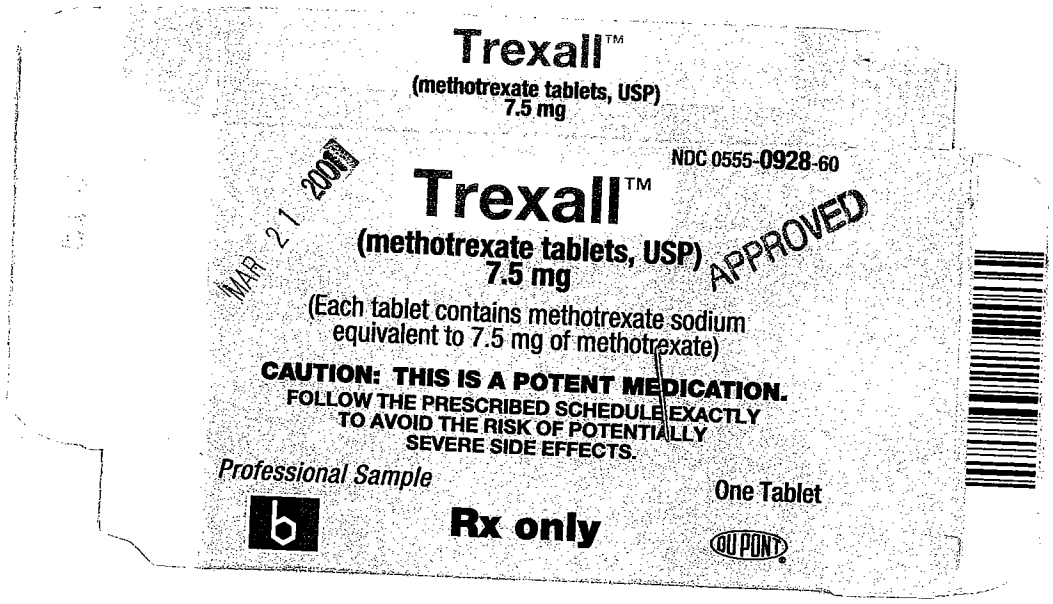

Each tablet contains methotrexate sodium equivalent to 15 mg of Methotrexate.
Caution: Pharmacist: Because of its potential to cause severe toxicity, methotrexate therapy requires close supervision of the patient by the physician. Prescriptions should not be written or refilled on a PRN basis. Refill of such prescriptions should be by direct order (written or oral) of the physician only. See Boxed Warnings for complete directions for use.
KEEP OUT OF THE REACH OF CHILDREN.
Dispense with a child-resistant closure in a well-closed container as defined in the USP.
Store at controlled room temperature 15°-30°C (59°-86°F).
Protect from light.
R9-00
2120945020101
Trexall
(methotrexate tablets, USP)
15 mg
Rx only
100 Tablets
Warning: Discontinue or reduce dosage immediately at first sign of ulceration or bleeding in mouth, gastrointestinal ulceration or bleeding, diarrhea or marked depression of bone marrow.
Usual Dosage:
See package brochure.
Manufactured by:
BARR LABORATORIES, INC.
Pomona, NY 10970
Marketed by:
DuPont Pharma
Wilmington, DE 19880
NDC 0555-0945-02
3 0555-0945-02 4
SAMPLE
Exp:
Lot:

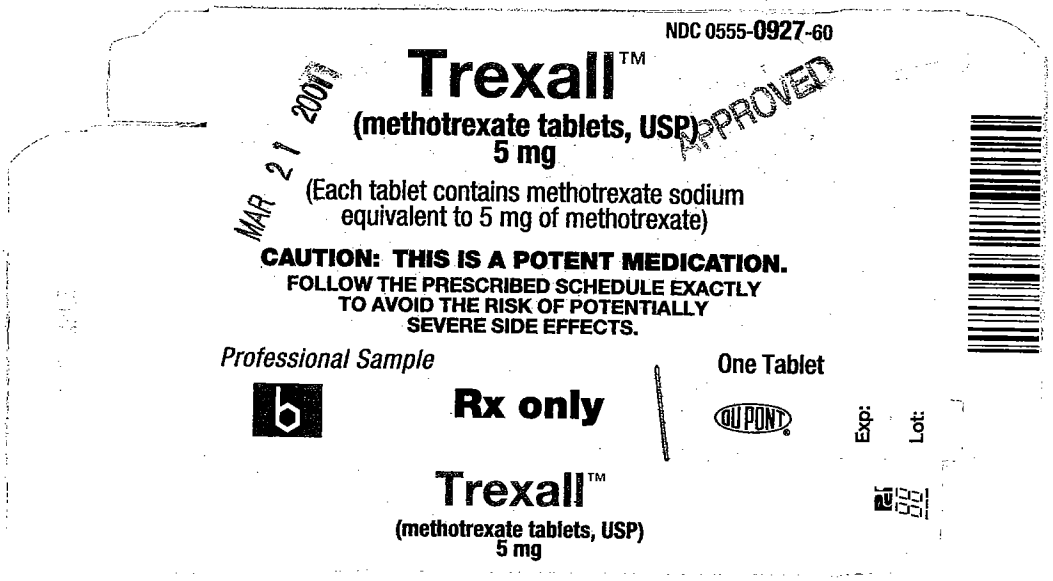

Each tablet contains methotrexate sodium equivalent to 15 mg of Methotrexate.
Caution: Pharmacist: Because of its potential to cause severe toxicity, methotrexate therapy requires close supervision of the patient by the physician. Prescriptions should not be written or refilled on a PRN basis. Refill of such prescriptions should be by direct order (written or oral) of the physician only. See Boxed Warnings for complete directions for use.
KEEP OUT OF THE REACH OF CHILDREN.
Dispense with a child-resistant closure in a well-closed container as defined in the USP.
Store at controlled room temperature 15°-30°C (59°-86°F).
Protect from light.
R9-00
2120945090101
Trexall
(methotrexate tablets, USP)
15 mg
Rx only
60 Tablets
Warning: Discontinue or reduce dosage immediately at first sign of ulceration or bleeding in mouth, gastrointestinal ulceration or bleeding, diarrhea or marked depression of bone marrow.
Usual Dosage:
See package brochure.
Manufactured by:
BARR LABORATORIES, INC.
Pomona, NY 10970
Marketed by:
DuPont Pharma
Wilmington, DE 19880
NDC 0555-0945-09
3 0555-0945-09 3
SAMPLE
Exp:
Lot:

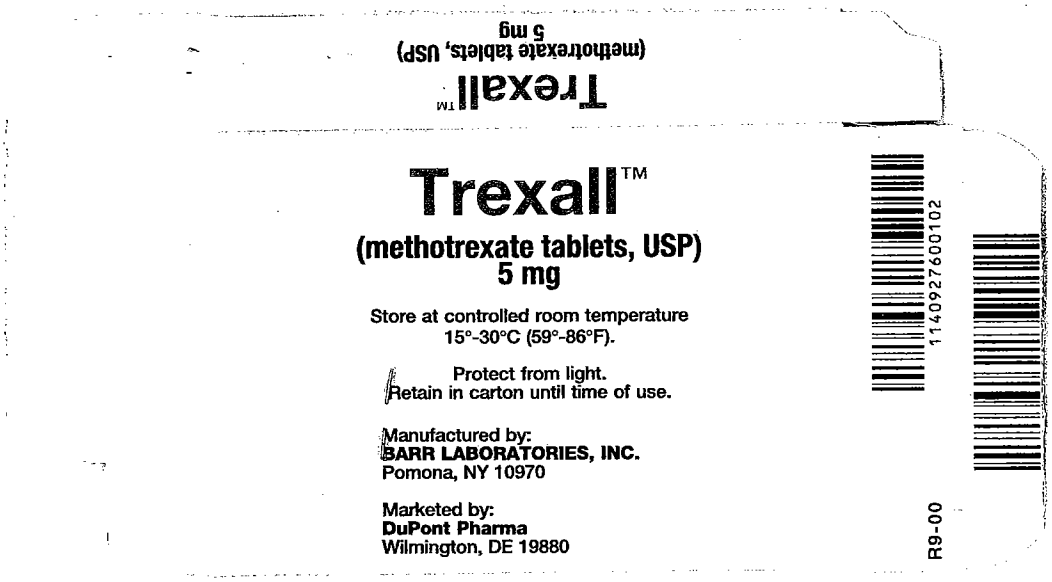

Each tablet contains methotrexate sodium equivalent to 15 mg of Methotrexate.
Caution: Pharmacist: Because of its potential to cause severe toxicity, methotrexate therapy requires close supervision of the patient by the physician. Prescriptions should not be written or refilled on a PRN basis. Refill of such prescriptions should be by direct order (written or oral) of the physician only. See Boxed Warnings for complete directions for use.
KEEP OUT OF THE REACH OF CHILDREN.
Dispense with a child-resistant closure in a well-closed container as defined in the USP.
Store at controlled room temperature 15°-30°C (59°-86°F).
Protect from light.
R9-00
2120945010101
Trexall
(methotrexate tablets, USP)
15 mg
Rx only
30 Tablets
Warning: Discontinue or reduce dosage immediately at first sign of ulceration or bleeding in mouth, gastrointestinal ulceration or bleeding, diarrhea or marked depression of bone marrow.
Usual Dosage:
See package brochure.
Manufactured by:
BARR LABORATORIES, INC.
Pomona, NY 10970
Marketed by:
DuPont Pharma
Wilmington, DE 19880
NDC 0555-0945-01
3 0555-0945-01 7
SAMPLE
Exp:
Lot:

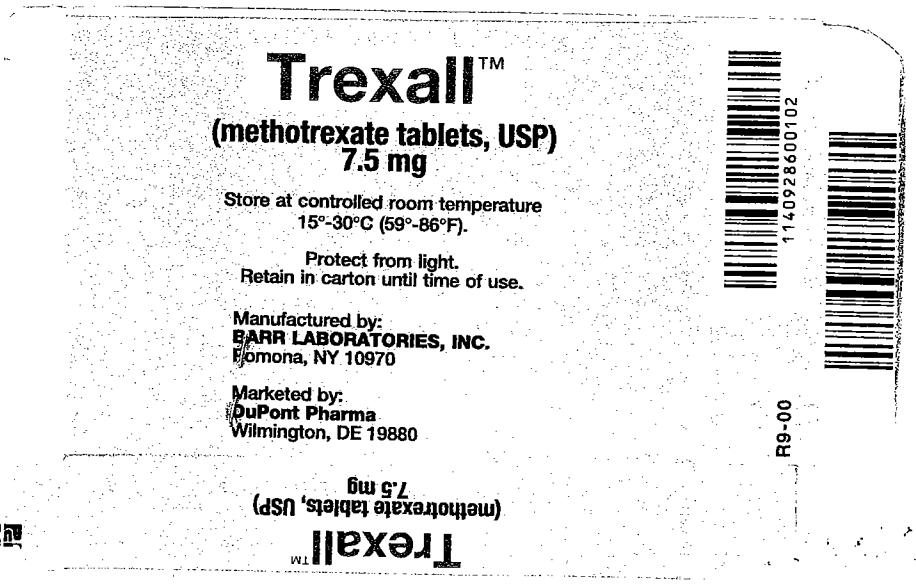

Each tablet contains methotrexate sodium equivalent to 15 mg of Methotrexate.
Caution: Pharmacist: Because of its potential to cause severe toxicity, methotrexate therapy requires close supervision of the patient by the physician. Prescriptions should not be written or refilled on a PRN basis. Refill of such prescriptions should be by direct order (written or oral) of the physician only. See Boxed Warnings for complete directions for use.
KEEP OUT OF THE REACH OF CHILDREN.
Dispense with a child-resistant closure in a well-closed container as defined in the USP.
Store at controlled room temperature 15°-30°C (59°-86°F).
Protect from light.
R9-00
2120945550101
Trexall
(methotrexate tablets, USP)
15 mg
PROFESSIONAL SAMPLE
Rx only
4 Tablets
Warning: Discontinue or reduce dosage immediately at first sign of ulceration or bleeding in mouth, gastrointestinal ulceration or bleeding, diarrhea or marked depression of bone marrow.
Usual Dosage:
See package brochure.
Manufactured by:
BARR LABORATORIES, INC.
Pomona, NY 10970
Marketed by:
DuPont Pharma
Wilmington, DE 19880
NDC 0555-0945-55
3 0555-0945-55 0
SAMPLE
Exp:
Lot:

40-385


Trexall™
(methotrexate tablets, USP)
7.5 mg
NDC 0555-0928-60
Trexall™
(methotrexate tablets, USP)
7.5 mg
MAR 21 2001
APPROVED
(Each tablet contains methotrexate sodium equivalent to 7.5 mg of methotrexate)
CAUTION: THIS IS A POTENT MEDICATION.
FOLLOW THE PRESCRIBED SCHEDULE EXACTLY TO AVOID THE RISK OF POTENTIALLY SEVERE SIDE EFFECTS.
Professional Sample
One Tablet
Rx only
DUPONT


NDC 0555-0927-60
Trexall™
(methotrexate tablets, USP)
5 mg
MAR 21 2001
APPROVED
(Each tablet contains methotrexate sodium equivalent to 5 mg of methotrexate)
CAUTION: THIS IS A POTENT MEDICATION.
FOLLOW THE PRESCRIBED SCHEDULE EXACTLY TO AVOID THE RISK OF POTENTIALLY SEVERE SIDE EFFECTS.
Professional Sample
One Tablet
Rx only
DUPONT
Exp:
Lot:
Trexall™
(methotrexate tablets, USP)
5 mg

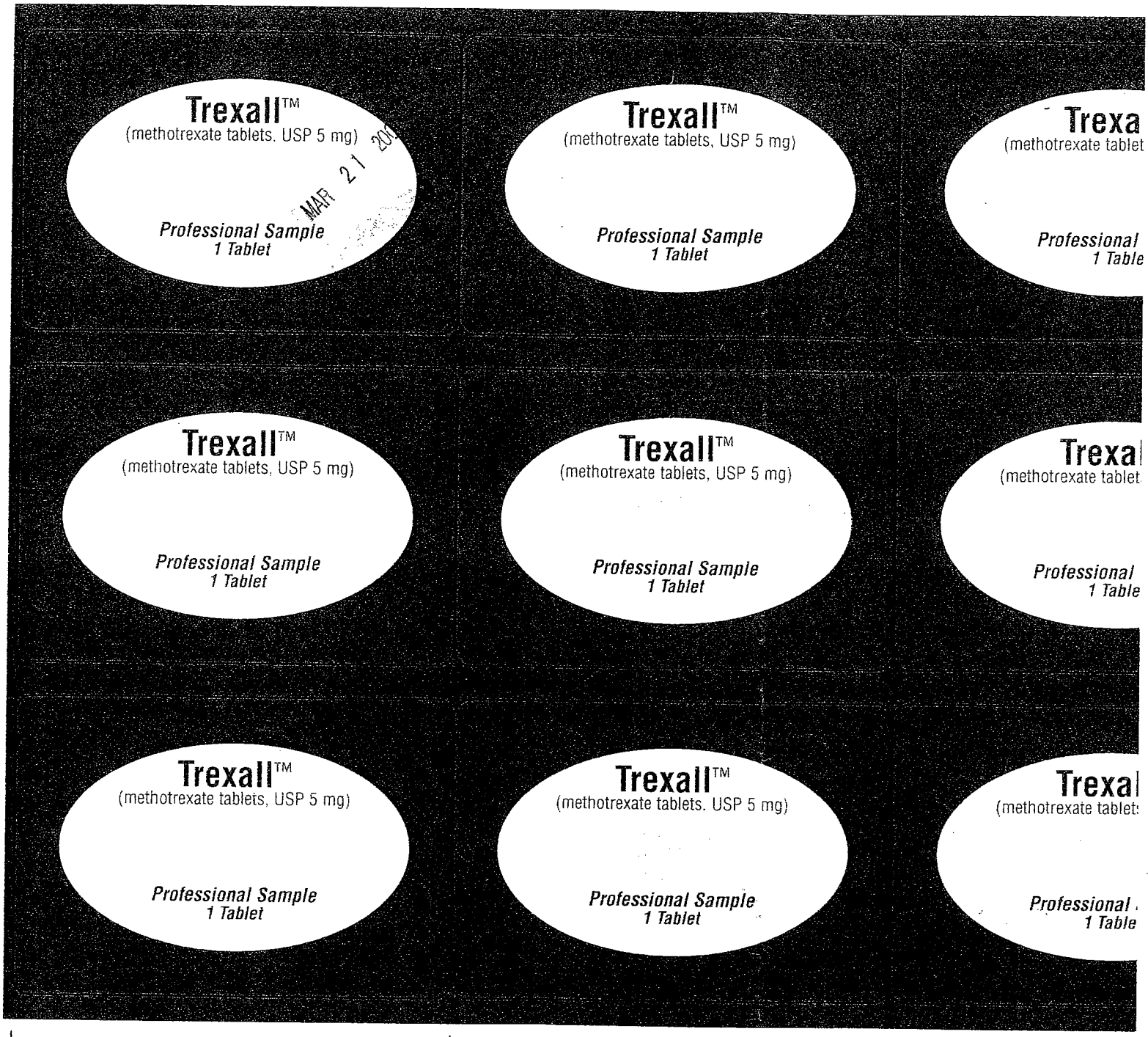

Trexall™
(methotrexate tablets, USP)
5 mg
Trexall™
(methotrexate tablets, USP)
5 mg
Store at controlled room temperature
15°-30°C (59°-86°F).
Protect from light.
Retain in carton until time of use.
Manufactured by:
BARR LABORATORIES, INC.
Pomona, NY 10970
Marketed by:
DuPont Pharma
Wilmington, DE 19880
11409276001 02
R9-00


Trexall™
(methotrexate tablets, USP)
7.5 mg
Trexall™
(methotrexate tablets, USP)
7.5 mg
Store at controlled room temperature
15°-30°C (59°-86°F).
Protect from light.
Retain in carton until time of use.
Manufactured by:
BARR LABORATORIES, INC.
Pomona, NY 10970
Marketed by:
DuPont Pharma
Wilmington, DE 19880
11409286001 02
R9-00

10-385

9 Labels

VINYL HEATSEAL (FRONT/FOIL) SIDE



3.125" 3.125" 3.125"

9.375"

8

GREEN
PMS 365

LAVENDAR
PMS 2573

NON-VINYL (BACK/PAPER) SIDE

(Each tablet contains methotrexate sodium equivalent to 5 mg of methotrexate)

CAUTION: THIS IS A POTENT MEDICATION. FOLLOW THE PRESCRIBED SCHEDULE EXACTLY TO AVOID THE RISK OF POTENTIALLY SEVERE SIDE EFFECTS.

Push through tablet from the other side.

Manufactured by:
BARR LABORATORIES, INC.
Pomona, NY 10970

Marketed by:
DuPont Pharma
Wilmington, DE 19880

R9-00

(Each tablet contains methotrexate sodium equivalent to 5 mg of methotrexate)

CAUTION: THIS IS A POTENT MEDICATION. FOLLOW THE PRESCRIBED SCHEDULE EXACTLY TO AVOID THE RISK OF POTENTIALLY SEVERE SIDE EFFECTS.

Push through tablet from the other side.

Manufactured by:
BARR LABORATORIES, INC.
Pomona, NY 10970

Marketed by:
DuPont Pharma
Wilmington, DE 19880

R9-00

(Each tablet contai
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CAUTION: THIS IS
THE PRESCRIBED
RISK OF POTENTI

Push through tabl

Manufactured by:
BARR LABORATO
Pomona, NY 1097

Marketed by:
DuPont Pharma
Wilmington, DE 1

R9-00

(Each tablet contains methotrexate sodium equivalent to 5 mg of methotrexate)

CAUTION: THIS IS A POTENT MEDICATION. FOLLOW THE PRESCRIBED SCHEDULE EXACTLY TO AVOID THE RISK OF POTENTIALLY SEVERE SIDE EFFECTS.

Push through tablet from the other side.

Manufactured by:
BARR LABORATORIES, INC.
Pomona, NY 10970

Marketed by:
DuPont Pharma
Wilmington, DE 19880

R9-00

(Each tablet contains methotrexate sodium equivalent to 5 mg of methotrexate)

CAUTION: THIS IS A POTENT MEDICATION. FOLLOW THE PRESCRIBED SCHEDULE EXACTLY TO AVOID THE RISK OF POTENTIALLY SEVERE SIDE EFFECTS.

Push through tablet from the other side.

Manufactured by:
BARR LABORATORIES, INC.
Pomona, NY 10970

Marketed by:
DuPont Pharma
Wilmington, DE 19880

R9-00

(Each tablet conta
to

CAUTION: THIS I
THE PRESCRIBE
RISK OF POTENT

Push through tab

Manufactured by:
BARR LABORAT
Pomona, NY 109

Marketed by:
DuPont Pharma
Wilmington, DE

R9-00

(Each tablet contains methotrexate sodium equivalent to 5 mg of methotrexate)

CAUTION: THIS IS A POTENT MEDICATION. FOLLOW THE PRESCRIBED SCHEDULE EXACTLY TO AVOID THE RISK OF POTENTIALLY SEVERE SIDE EFFECTS.

Push through tablet from the other side.

Manufactured by:
BARR LABORATORIES, INC.
Pomona, NY 10970

Marketed by:
DuPont Pharma
Wilmington, DE 19880

R9-00

(Each tablet contains methotrexate sodium equivalent to 5 mg of methotrexate)

CAUTION: THIS IS A POTENT MEDICATION. FOLLOW THE PRESCRIBED SCHEDULE EXACTLY TO AVOID THE RISK OF POTENTIALLY SEVERE SIDE EFFECTS.

Push through tablet from the other side.

Manufactured by:
BARR LABORATORIES, INC.
Pomona, NY 10970

Marketed by:
DuPont Pharma
Wilmington, DE 19880

R9-00

(Each tablet cont
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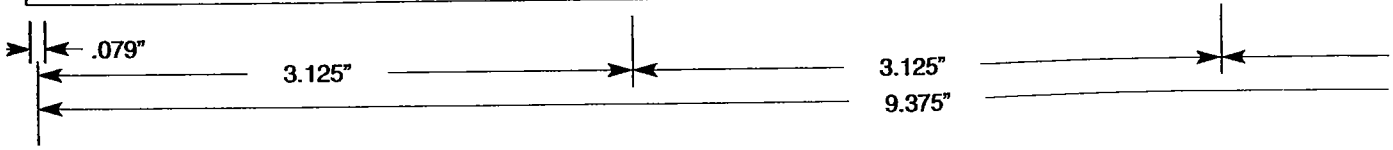
CAUTION: THIS
THE PRESCRIBE
RISK OF POTEN

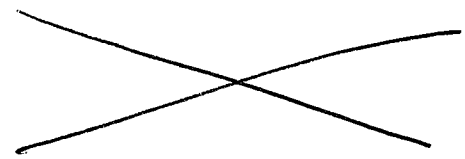
Push through ta

Manufactured by
BARR LABORAT
Pomona, NY 10

Marketed by:
DuPont Pharma
Wilmington, DE

R9-00





40-385

NDC 0555-**0927**-60

Trexall™

(methotrexate tablets, USP)
5 mg

(Each tablet contains methotrexate sodium equivalent to 5 mg of methotrexate)

NDC 0555-**0927**-60

Trexall™

(methotrexate tablets, USP)
5 mg

(Each tablet contains methotrexate sodium equivalent to 5 mg of methotrexate)

CAUTION: THIS IS A POTENT MEDICATION. FOLLOW THE PRESCRIBED SCHEDULE EXACTLY TO AVOID THE RISK OF POTENTIALLY SEVERE SIDE EFFECTS.

SAMPLE

MAR 21 2000
APPROVED

Rx only

Professional Samples

10 Samples x 1
5 mg Tablet

DUPONT®

R9-00
2140927600102

NDC 0555-**0927**-60

Trexall™

(methotrexate tablets, USP)
5 mg

(Each tablet contains methotrexate sodium equivalent to 5 mg of methotrexate)

10 Samples x 1
5 mg Tablet

Trexall™

(methotrexate tablets, USP)
5 mg

(Each tablet contains methotrexate sodium equivalent to 5 mg of methotrexate)

Usual Dosage: See package brochure.

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

Protect from light.

Retain in carton until time of use.

Professional Samples

10 Samples x 1
5 mg Tablet

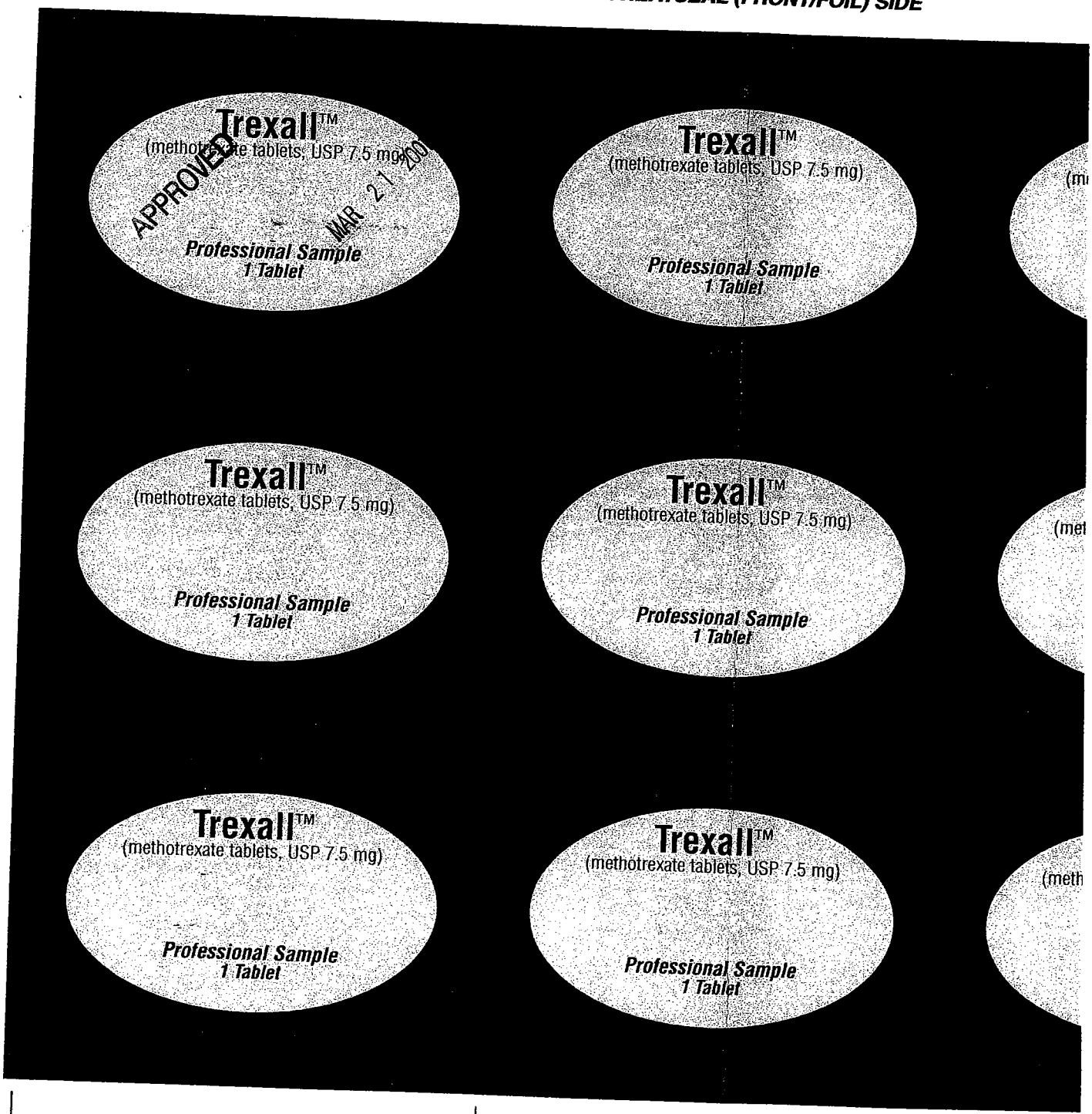
Manufactured by:
BARR LABORATORIES, INC.
Pomona, NY 10970

Marketed by:
DuPont Pharma
Wilmington, DE 19880

40-385

9L

VINYL HEATSEAL (FRONT/FOIL) SIDE



3.125" 3.125"

9.375"

8

3

NON-VINYL (BACK/PAPER) SIDE

sodium equivalent
rexate)

ICATION. FOLLOW
CTLY TO AVOID THE
DE EFFECTS.

side.

(Each tablet contains methotrexate sodium equivalent to 7.5 mg of methotrexate)

CAUTION: THIS IS A POTENT MEDICATION. FOLLOW THE PRESCRIBED SCHEDULE EXACTLY TO AVOID THE RISK OF POTENTIALLY SEVERE SIDE EFFECTS.

Push through tablet from the other side.

Manufactured by:
BARR LABORATORIES, INC.
Pomona, NY 10970

Marketed by:
DuPont Pharma
Wilmington, DE 19880

R9-00

(Each tablet contains methotrexate sodium equivalent to 7.5 mg of methotrexate)

CAUTION: THIS IS A POTENT MEDICATION. FOLLOW THE PRESCRIBED SCHEDULE EXACTLY TO AVOID THE RISK OF POTENTIALLY SEVERE SIDE EFFECTS.

Push through tablet from the other side.

Manufactured by:
BARR LABORATORIES, INC.
Pomona, NY 10970

Marketed by:
DuPont Pharma
Wilmington, DE 19880

R9-00

sodium equivalent
exate)

CATION. FOLLOW
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E EFFECTS.

side.

(Each tablet contains methotrexate sodium equivalent to 7.5 mg of methotrexate)

CAUTION: THIS IS A POTENT MEDICATION. FOLLOW THE PRESCRIBED SCHEDULE EXACTLY TO AVOID THE RISK OF POTENTIALLY SEVERE SIDE EFFECTS.

Push through tablet from the other side.

Manufactured by:
BARR LABORATORIES, INC.
Pomona, NY 10970

Marketed by:
DuPont Pharma
Wilmington, DE 19880

R9-00

(Each tablet contains methotrexate sodium equivalent to 7.5 mg of methotrexate)

CAUTION: THIS IS A POTENT MEDICATION. FOLLOW THE PRESCRIBED SCHEDULE EXACTLY TO AVOID THE RISK OF POTENTIALLY SEVERE SIDE EFFECTS.

Push through tablet from the other side.

Manufactured by:
BARR LABORATORIES, INC.
Pomona, NY 10970

Marketed by:
DuPont Pharma
Wilmington, DE 19880

R9-00

odium equivalent
xate)

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E EFFECTS.

ide.

(Each tablet contains methotrexate sodium equivalent to 7.5 mg of methotrexate)

CAUTION: THIS IS A POTENT MEDICATION. FOLLOW THE PRESCRIBED SCHEDULE EXACTLY TO AVOID THE RISK OF POTENTIALLY SEVERE SIDE EFFECTS.

Push through tablet from the other side.

Manufactured by:
BARR LABORATORIES, INC.
Pomona, NY 10970

Marketed by:
DuPont Pharma
Wilmington, DE 19880

R9-00

(Each tablet contains methotrexate sodium equivalent to 7.5 mg of methotrexate)

CAUTION: THIS IS A POTENT MEDICATION. FOLLOW THE PRESCRIBED SCHEDULE EXACTLY TO AVOID THE RISK OF POTENTIALLY SEVERE SIDE EFFECTS.

Push through tablet from the other side.

Manufactured by:
BARR LABORATORIES, INC.
Pomona, NY 10970

Marketed by:
DuPont Pharma
Wilmington, DE 19880

R9-00

3.125"

3.125"

9.375"

3

NDC 0555-**0928**-60

Trexall™

(methotrexate tablets, USP)
7.5 mg

(Each tablet contains methotrexate sodium equivalent to 7.5 mg of methotrexate)

NDC 0555-**0928**-60

Trexall™

(methotrexate tablets, USP)
7.5 mg

(Each tablet contains methotrexate sodium equivalent to 7.5 mg of methotrexate)

CAUTION: THIS IS A POTENT MEDICATION. FOLLOW THE PRESCRIBED SCHEDULE EXACTLY TO AVOID THE RISK OF POTENTIALLY SEVERE SIDE EFFECTS.

Rx only

Professional Samples 10 Samples x 1
7.5 mg Tablet

DUPONT®

Pull tab to open

R9-00
21409286001102

NDC 0555-**0928**-60

Trexall™

(methotrexate tablets, USP)
7.5 mg

(Each tablet contains methotrexate sodium equivalent to 7.5 mg of methotrexate)

10 Samples x 1
7.5 mg Tablet

Trexall™

(methotrexate tablets, USP)
7.5 mg

(Each tablet contains methotrexate sodium equivalent to 7.5 mg of methotrexate)

Usual Dosage: See package brochure.

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

Protect from light.

Retain in carton until time of use.

Professional Samples **10 Samples x 1**
7.5 mg Tablet

Manufactured by:
BARR LABORATORIES, INC.
Pomona, NY 10970

Marketed by:
DuPont Pharma
Wilmington, DE 19880

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-385

LABELING REVIEW(S)

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

ANDA Number: 40-385 **Date of Submission: July 23, 1999**
Applicant's Name: Barr Laboratories, Inc.
Established Name: Methotrexate Tablets USP, 5 mg and 15 mg
Proposed Proprietary Name: ————
Labeling Deficiencies:

1. GENERAL COMMENTS – Your proposed proprietary name has been found unacceptable based on 21 CFR 201.10(c)(5). It sounds like or looks like the following proprietary names already on the market: Mesnex® and Mezlin®. Please remove it from all labels and labeling.

2. CONTAINER (30's and 60's)

   i. Caution- Revise the second and third sentences in this section to read as follows:

   Prescriptions should not be written or refilled on a PRN basis. Refill of prescriptions should be by direct order (written or oral) of the physician only. See Boxed Warnings for complete directions for use.

   ii. Include the statement "KEEP OUT OF REACH OF CHILDREN."

3. UNIT DOSE BLISTER (1's)- See comment under GENERAL COMMENTS.

4. UNIT DOSE BLISTER CARTON (1 x 5 mg, and ' ———)- See comments under GENERAL COMMENTS and (ii) under CONTAINER.

5. PROFESSIONAL SAMPLE DISPENSER (10 x 1[5 mg] and ' ———)- See comments under GENERAL COMMENTS and (ii) under CONTAINER.
6. INSERT
   a. Revise your insert to be in accord with the most recent labeling for the reference listed drug, Methotrexate Tablets USP (Lederle; NDA# 08-085/S0048; approved October 29, 1999). The labeling may be obtained from Freedom of Information or the following website – http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html.
   b. See comment under GENERAL COMMENTS.

Please revise your labels and labeling, as instructed above, and submit 4 copies of draft labels and labeling. We will not request final print labels and labeling until a determination has been made regarding the acceptability of your proposed proprietary name.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes- http://www.fda.gov/cder/ogd/rld/labeling_review_branch.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 the reference listed drug labeling with all differences annotated and explained.

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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: (30's and 60's)
Unit Dose Blister (1's)
Unit Dose Blister Carton (1 x 5 mg, and ' ———

Physician's sample Dispenser (10 x 1[5 mg] and ———— Satisfactory as of July 23, 1999 submission.

Professional Package Insert Labeling: Satisfactory as of July 23, 1999 submission.

Revisions needed post-approval:

BASIS OF APPROVAL:
Was this approval based upon a petition? Yes
What is the RLD on the 356(h) form: Methotrexate Sodium Tablets

NDA Number: 08-085/S-048
NDA Drug Name: Methotrexate Sodium Tablets
NDA Firm: Lederle Laboratories

Date of Approval of NDA Insert and supplement #: October 29, 1999
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.

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 23	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	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)	**Yes**	**No**	**N.A.**
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	
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	

FOR THE RECORD:

1. The reference listed drug for this product is Methotrexate Sodium Tablets, 2.5 mg (Lederle; NDA#08-085/S-048; Approved October 29, 1999.
2. The firm cites suitability petition docket number 97P-0279/CP1, approved August 22, 1997, as the basis for the 5 mg and 15 mg strength submission. See Vol. 1.1, page 02-00005.
3. The firm certifies there are no patents/exclusivities in effect for this drug product. See Vol. 1.1, page 03-00001.
4. The product is manufactured by Barr Laboratories, Inc., 2150 Perrowville Road, Forest, VA 24551. See Vol. 1.2, page 09-00002.
5. Outside firms are utilized for testing only. See Vol. 1.2, page 10-00002.
6. Container/Closure

   30's – bottle: 75 cc, HDPE, White, Wide mouth, Round 33/400,
   Cap: Metal, with Inner liner 33/400, (Two-piece ' ——— CRC)
   Filler: 12 grams cotton

   60's (5mg)- bottle: 75 cc, HDPE, White, Wide mouth, Round 33/400
   Cap: Metal, with Inner liner 33/400, (Two-piece ' ——— CRC)
   Filler: 12 grams cotton

   60's (15mg)- bottle: 120 cc HDPE, White, Wide mouth, Round 38/400
   Cap: Metal with ' ——, 38/400
   Filler: 16 grams cotton

   1 Tablet Blister Card for 5 mg and ' —— strength Physician sample :
   Film: ————————
   Foil: ———— , aluminum foil, ————————
   See Vol. 1.3, page 13-00003.
7. Product Line:
   2.5 mg – (36's, 100's, 500's, and a Dose pack) [approved under separate ANDA]
   5 mg - (30's and 60's)
   15 mg – (30's and 60's)
   See Vol. 1.1, page 05-00016.

8. Components/Composition
Innovator:
Active: Methotrexate Sodium equivalent to 2.5 mg Methotrexate
Inactive: Lactose
Magnesium Stearate
Pregelatinized Starch
And possibly corn starch
Applicant:
Active: Methotrexate 5 mg or 15 mg
Inactive:Sodium Carbonate
Microcrystalline Cellulose
Anhydrous Lactose
Pregelatinized Starch
Crospovidone
Talc
Magnesium Stearate
5 mg only – [redacted] titanium dioxide, polyethylene glycol, FD&C Blue No 1 aluminum lake, Polysorbate 80, D&C Yellow No 10 aluminum lake, FD&C Yellow No 6 aluminum lake)
15 mg only-[redacted] titanium dioxide,[redacted], FD&C Blue No 2 aluminum lake, FD&C Red No 40 aluminum lake, Polysorbate 80)
See Vol. 1.1, page 07-0002

9. Storage/Dispensing
NDA: Store at 25°C (77°F); excursions permitted to 15° - 30°C (59° - 86°F) [see USP controlled Room Temperature]. Protect from light.
ANDA: Dispense with a child-resistant closure in a well-closed container as defined in USP. Store at controlled room temperature 15° - 30°C (59° - 86°F). Protect from light.
USP: Preserve in well-closed containers. A unit-of-use container contains a quantity of tablets sufficient to provide one week's therapy as indicated in the labeling.
Labeling: When packaged in a unit-of-use container, the label indicates the total amount of methotrexate present as one week's supply. See Vol. 1.1, page 05-00016.

Date of Review: September 22, 1999
Date of Submission: July 23, 1999

Reviewer: JWatkins **Date:** 12/21/99

Team Leader: [signature] **Date:** 12/21/1999

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cc:
ANDA: 40-385
DUP/DIVISION FILE
HFD-613/TWatkins/JGrace (no cc)
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Review

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

ANDA Number: 40-385 **Date of Submission: April 14, 2000**
Applicant's Name: Barr Laboratories, Inc.
Established Name: Methotrexate Tablets USP, 5 mg, 7.5 mg, 10mg and 15 mg
Proposed Proprietary Name: ———, TREXALL™, and ———
Labeling Deficiencies:

1. GENERAL COMMENTS – Your proposed proprietary names are under review. We defer comment at this time.

2. CONTAINER (30's, 60's and 100's)
   i. Storage Temperature Recommendation- include "Protect from light.".
   ii. Warnings- Delete " ———

3. PHYSICIAN'S SAMPLE BOTTLE (4's) – See comments under CONTAINER.

4. PHYSICIAN'S SAMPLE UNIT DOSE BLISTER (1's)- See GENERAL COMMENTS.

5. PHYSICIAN'S SAMPLE UNIT DOSE BLISTER CARTON (1's)- See GENERAL COMMENTS.

6. PHYSICIAN'S SAMPLE DISPENSER (10 unit dose cartons per dispenser)-See comments under GENERAL COMMENTS.

7. INSERT
   a. See GENERAL COMMENTS.
   b. INDICATIONS AND USAGE
      i. Neoplastic Diseases – Delete ———
   c. PRECAUTIONS (Information for Patients) – Second paragraph- Delete the penultimate sentence which reads, " ——— Your product is not ———
   d. PRECAUTIONS (Organ System Toxicity; Neurologic) – Include the following to appear as the second and third sentences of paragraph one of this subsection:

      Serious neurotoxicity, frequently manifested as generalized or focal seizures, has been reported with unexpectedly increased frequency among pediatric patients with acute lymphoblastic leukemia who were treated with intermediate-dose intravenous methotrexate (1 gm/m^2). Symptomatic patients were commonly noted to have leukoencephalopathy and/or microangiopathic calcifications on diagnostic imaging studies.

      NOTE: Although you are not seeking approval for the indication referenced above, we feel that it is important information for safe use of the drug. Although seizures are only documented in this situation, it may be reasonable that this could occur in other situations.

   e. ADVERSE REACTIONS (Adverse reactions in Psoriasis) – Include the following to appear as the last sentence in this subsection:

      Rarely, painful plaque erosions may appear (Pearce, HP and Wilson, BB: *Am Acad Dermatol* 35" 835-838, 1996).

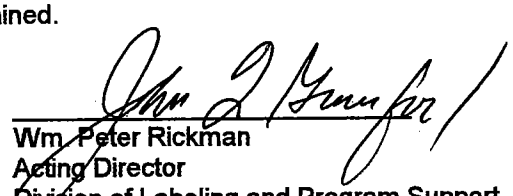
f. DOSAGE AND ADMINISTRATION (Psoriasis and Rheumatoid Arthritis) Revise the second paragraph of this subsection to read as follows:

Weekly therapy may be instituted to provide doses over a range of 5 mg to 15 mg administered as a single weekly dose. All schedules should be continually tailored to the individual patient. An initial test dose may be given prior to the regular dosing schedule to detect any extreme sensitivity to adverse effects (see **ADVERSE REACTIONS**). Maximal myelosuppression usually occurs in seven to ten days.

Please revise your labels and labeling, as instructed above, and submit 4 copies of draft labels and labeling. We will not request final print labels and labeling until a determination has been made regarding the acceptability of your proposed proprietary name.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes- http://www.fda.gov/cder/ogd/rld/labeling_review_branch.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 the reference listed drug labeling with all differences annotated and explained.



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

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: (30's, 60's and 100's)
Professional sample bottle labels (4's)
Unit Dose Blister (1's)
Unit Dose Blister Carton (1 tablet per carton)
Physician's sample Dispenser (10 Unit dose cartons per dispenser) Satisfactory as of July 23, 1999 submission.
Professional Package Insert Labeling: Satisfactory as of July 23, 1999 submission.

BASIS OF APPROVAL:
Was this approval based upon a petition? Yes
What is the RLD on the 356(h) form: Methotrexate Sodium Tablets
NDA Number: 08-085/S-048
NDA Drug Name: Methotrexate Sodium Tablets
NDA Firm: Lederle Laboratories
Date of Approval of NDA Insert and supplement #: October 29, 1999
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.

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 23	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)	**Yes**	**No**	**N.A.**
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	
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	

FOR THE RECORD:

1. The reference listed drug for this product is Methotrexate Sodium Tablets, 2.5 mg (Lederle; NDA#08-085/S-048; Approved October 29, 1999.
2. The firm cites suitability petition docket number 97P-0279/CP1, approved August 22, 1997, as the basis for the 5 mg, 7.5 mg,10 mg and 15 mg strength submission. See Vol. 1.1 & 4.1, page 02-00005.
3. The firm certifies there are no patents/exclusivities in effect for this drug product. See Vol. 1.1, page 03-00001.
4. The product is manufactured by Barr Laboratories, Inc., 2150 Perrowville Road, Forest, VA 24551. See Vol. 1.2, page 09-00002.
5. Outside firms are utilized for testing only. See Vol. 1.2, page 10-00002.
6. Container/Closure
   30's – bottle: 75 cc, HDPE, White, Wide mouth, Round 33/400, Cap: Metal, with Inner liner 33/400, (Two-piece ——— CRC), Filler: 12 grams cotton
   60's (5mg)- bottle: 75 cc, HDPE, White, Wide mouth, Round 33/400, Cap: Metal, with Inner liner 33/400, (Two-piece ——— CRC), Filler: 12 grams cotton
   60's (15mg)- bottle: 120 cc HDPE, White, Wide mouth, Round 38/400, Cap: Metal with ——., 38/400 Filler: 16 grams cotton
   1 Tablet Blister Card for 5 mg and ——— strength Physician sample : Film: ——— ———, Foil: ——— aluminum foil, ——— . See Vol. 1.3, page 13-00003.
7. Product Line:
   2.5 mg – (36's, 100's, 500's, and a Dose pack) [approved under separate ANDA]
   5 mg - (30's, 60's and 100's) plus physician's sample bottle of 4's and unit dose blister of 1's.
   7.5 mg- (30's, 60's and 100's) plus physician's sample bottle of 4's and unit dose blister of 1's.
   10 mg- 30's, 60's and 100's) plus physician's sample bottle of 4's ———
   15 mg – (30's and 60's) plus physician's sample bottle of 4's ———
   See Vol. 1.1, page 05-00016.
8. Components/Composition
   Innovator:
   Active: Methotrexate Sodium equivalent to 2.5 mg Methotrexate
   Inactive: Lactose, Magnesium Stearate, Pregelatinized Starch, And possibly corn starch
   Applicant:
   Active: Methotrexate 5 mg or 15 mg
   Inactive:Sodium Carbonate, Microcrystalline Cellulose, Anhydrous Lactose, Pregelatinized Starch, Crospovidone, Talc, Magnesium Stearate
   5 mg only – ——— titanium dioxide, ——— FD&C Blue No 1 aluminum lake, Polysorbate 80, D&C Yellow No 10 aluminum lake, FD&C Yellow No 6 aluminum lake)
   15 mg only- ——— , titanium dioxide, ——— FD&C Blue No 2 aluminum lake, FD&C Red No 40 aluminum lake, Polysorbate 80)
   See Vol. 1.1, page 07-0002
9. Storage/Dispensing
   NDA: Store at 25°C (77°F); excursions permitted to 15° - 30°C (59° - 86°F) [see USP controlled Room

Temperature]. Protect from light.
ANDA: Dispense with a child-resistant closure in a well-closed container as defined in USP. Store at controlled room temperature 15° - 30°C (59° - 86°F). Protect from light.
USP: Preserve in well-closed containers. A unit-of-use container contains a quantity of tablets sufficient to provide one week's therapy as indicated in the labeling.
Labeling: When packaged in a unit-of-use container, the label indicates the total amount of methotrexate present as one week's supply. See Vol. 1.1, page 05-00016.

Date of Review: April 19, 2000
Date of Submission: April 14, 2000

Reviewer: J. Watkins **Date:** 5/3/2000
Team Leader: **Date:** 5-17-2000

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cc: ANDA: 40-385
DUP/DIVISION FILE
HFD-613/TWatkins/JGrace (no cc)
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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: 40-385 Date of Submission: Jan. 12, 2001 & Feb 2, 2001
Applicant's Name: Barr Laboratories, Inc.
Established Name: Methotrexate Tablets USP, 5 mg, 7.5 mg, 10mg and 15 mg
Proprietary Name: TREXALL™

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? Yes TRADE NAME "TREXALL" APPROVED BY AGENCY.

Container Labels: 5 mg, 7.5 mg, 10 mg, 15 mg (30's, 60's and 100's)- Satisfactory in FPL as of Jan. 12, 2001.

Professional sample bottle labels (4's): 5 mg, 7.5 mg, 10 mg, 15 mg (4's) Satisfactory in FPL as of Jan. 12, 2001.

Professional sample Unit Dose Blister: 5 mg, 7.5 mg (1's) Satisfactory in FPL as of Jan. 12, 2001.

Professional sample Unit Dose Blister Carton: 5 mg, 7.5 mg (1 tablet per carton) Satisfactory in FPL as of Jan. 12, 2001.

Physician's sample Dispenser (10 Unit dose cartons per dispenser): 5 mg, 7.5 mg- Satisfactory in FPL as of Jan. 12, 2001

Professional Package Insert Labeling: (R /Jan2001) Satisfactory in FPL as of February 2, 2001
Revision needed post approval: Revise according to S-046/ AP 11/8/2000 or latest approved.
BASIS OF APPROVAL:
Was this approval based upon a petition? Yes
What is the RLD on the 356(h) form: Methotrexate Sodium Tablets
NDA Number: 08-085/S-048. CSO cannot provide S-046 make changes post approval.
NDA Drug Name: Methotrexate Sodium Tablets
NDA Firm: Lederle Laboratories
Date of Approval of NDA Insert and supplement #: October 29, 1999
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.

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 23	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)	Yes	No	N.A.
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	
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	

FOR THE RECORD:

1. The reference listed drug for this product is Methotrexate Sodium Tablets, 2.5 mg (Lederle; NDA#08-085/S-048; Approved October 29, 1999. CSO cannot provide S-046 at this time more changes and FPL needed of RLD.
2. The firm cites suitability petition docket number 97P-0279/CP1, approved August 22, 1997, as the basis for the 5 mg, 7.5 mg,10 mg and 15 mg strength submission. See Vol. 1.1 & 4.1, page 02-00005.
3. The firm certifies there are no patents/exclusivities in effect for this drug product. See Vol. 1.1, page 03-00001.
4. The product is manufactured by Barr Laboratories, Inc., 2150 Perrowville Road, Forest, VA 24551. See Vol. 1.2, page 09-00002.
5. Outside firms are utilized for testing only. See Vol. 1.2, page 10-00002.
6. Container/Closure
   30's – bottle: 75 cc, HDPE, White, Wide mouth, Round 33/400, Cap: Metal, with Inner liner 33/400, (Two-piece ——— CRC), Filler: 12 grams cotton
   60's (5mg)- bottle: 75 cc, HDPE, White, Wide mouth, Round 33/400, Cap: Metal, with Inner liner 33/400, (Two-piece ——— CRC), Filler: 12 grams cotton
   60's (15mg)- bottle: 120 cc HDPE, White, Wide mouth, Round 38/400, Cap: Metal with ——— 38/400 Filler: 16 grams cotton
   1 Tablet Blister Card for 5 mg ——— strength Physician sample : Film: ——— ———, Foil: ——— aluminum foil, ——— See Vol. 1.3, page 13-00003.

7. Product Line:
   2.5 mg – (36's, 100's, 500's, and a Dose pack) [approved under separate ANDA]
   5 mg - (30's, 60's and 100's) plus physician's sample bottle of 4's and unit dose blister of 1's.
   7.5 mg- (30's, 60's and 100's) plus physician's sample bottle of 4's and unit dose blister of 1's.
   10 mg- 30's, 60's and 100's) plus Dr. sample bottle of 4's and unit dose blister of 1's. Deleted ——— 1/12/01
   15 mg – (30's and 60's) plus Dr. sample bottle of 4's and unit dose blister of 1's. Deleted ———and added 100s
   See Vol. 1.1, page 05-00016. January 12, 2001
8. Components/Composition
   Innovator:
   Active: Methotrexate Sodium equivalent to 2.5 mg Methotrexate
   Inactive: Lactose, Magnesium Stearate, Pregelatinized Starch, And possibly corn starch
   Applicant:
   Active: Methotrexate 5 mg or 15 mg
   Inactive:Sodium Carbonate, Microcrystalline Cellulose, Anhydrous Lactose, Pregelatinized Starch, Crospovidone, Talc, Magnesium Stearate
   5 mg only – ———————————————, titanium dioxide, ———————
   FD&C Blue No 1 aluminum lake, Polysorbate 80, D&C Yellow No 10 aluminum lake, FD&C Yellow No 6 aluminum lake)
   15 mg only- ———————————————— titanium dioxide, ———————
   FD&C Blue No 2 aluminum lake, FD&C Red No 40 aluminum lake, Polysorbate 80)
   See Vol. 1.1, page 07-0002
9. Storage/Dispensing
   NDA: Store at 25°C (77°F); excursions permitted to 15° - 30°C (59° - 86°F) [see USP controlled Room Temperature]. Protect from light.
   ANDA: Dispense with a child-resistant closure in a well-closed container as defined in USP. Store at controlled room temperature 15° - 30°C (59° - 86°F). Protect from light.
   USP: Preserve in well-closed containers. A unit-of-use container contains a quantity of tablets sufficient to provide one week's therapy as indicated in the labeling.
   Labeling: When packaged in a unit-of-use container, the label indicates the total amount of methotrexate present as one week's supply. See Vol. 1.1, page 05-00016.
10. The professional sample sizes are not listed in the HOW SUPPLIED section of the insert.
11. Theresa apparently called the firm on August 8, 200 to inform the applicant that their trade name Trexall was accepted by the Agency. The applicant reconfirmed by calling in November 16, 2000. Theresa confirmed the acceptability of trexall. See vol 5.1 response form applicant. Writer unable to find record of telephone conversation or Agency approval letter. Will accept the response from applicant at this time.

Date of Review: Jan. 31, 2001 & Feb. 8, 2001 **Date of Submission: Jan. 12, 2001 & Feb 2, 2001**
Reviewer: Angela Payne **Date: 1/31/01 & 2/8/2001**
Team Leader: John Grace **Date:**

John Grace 2/12/2001

cc: ANDA: 40-385
DUP/DIVISION FILE
HFD-613/APayne/JGrace (no cc)
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Review

A Payne 2/8/01

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-385

CHEMISTRY REVIEW(S)

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1. CHEMISTRY REVIEW NO. 1

2. ANDA # **40385**

3. NAME AND ADDRESS OF APPLICANT
Barr Laboratories, Inc.
Attention: Christine Mundkur
2 Quaker Road
PO Box 2900
Pomona, NY 10970-0519

4. LEGAL BASIS FOR SUBMISSION
ANDA Suitability Petition for change in strength
Innovator Product: Methotrexate Sodium Tablets, 2.5 mg (base)
Innovator Company: ESI Lederle Inc., NDA 8085
Patent Expiration Date: Past
Exclusivity: None

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
——— However, the labeling reviewer will inform Barr that the proposed proprietary name is unacceptable.

7. NONPROPRIETARY NAME
Methotrexate Tablets, USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Vol.	Submission date	Submission type
A1.1 – 1.10 (A1.2 – 1.7 are Bio)	**07/23/99**	**Original**
A2.1	**08/06/99**	**NC – CMC electronic submission**
"	**09/08/99**	**Telecon re Bio facilities**
"	**09/20/99**	**NC – List of Bio facilities**
"	**09/21/99**	**"Acceptable for Filing" letter**
A3.1	**10/07/99**	**Bio telephone amendment**

10. PHARMACOLOGICAL CATEGORY
antineoplastic, antirheumatic and antipsoriatic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

Approved ANDA 81-099, Methotrexate Tablets USP, 2.5 mg, Barr Laboratories, Inc.

Bio-IND 15-304, Methotrexate Tablets USP, 15 mg, Barr Laboratories, Inc.

DMF number	DMF type	DMF holder	LOA(s)
	III: Packaging		
	III: Packaging		
	III: Packaging		
	III: Packaging		
	II: Drug Substance		
	III: Packaging		
	III: Packaging		
	III: Packaging		
	III: Packaging		
	III: Packaging		

See DMF Checklist for further details.

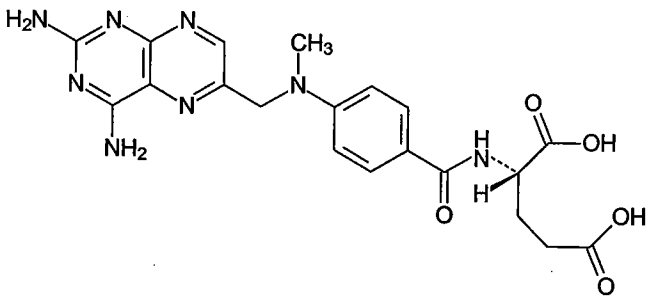
13. DOSAGE FORM
tablet

14. STRENGTH

Strength	Strength units
15	mg (base)
5	mg (base)

15. CHEMICAL NAME AND STRUCTURE

Methotrexate. L-Glutamic acid, *N*-[4-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-. $C_{20}H_{22}N_8O_5$. 454.45. 59-05-2.



16. RECORDS AND REPORTS N/A

17. COMMENTS

There are **deficiencies** in the following Review Points:

23.A, 23.B, 25, 28.A, 28.B, 29

The conditions of the **other disciplines** are as follows:

25. MANUFACTURING AND PROCESSING (Microbiology)

This is not a sterile product.

31. SAMPLES AND RESULTS

The drug substance and drug product are in USP 24.

32. LABELING

The labeling in the original submission was found **not satisfactory** by Ms. Teresa Watkins 12/21/99. Vol. A1.1

33. ESTABLISHMENT INSPECTION

An EER was submitted 9/21/99. The facilities were found **acceptable** 2/28/2000.

34. BIOEQUIVALENCE STATUS

The Bio review has not been completed, as of 2/28/2000.

18. CONCLUSIONS AND RECOMMENDATIONS

ANDA 40-385 is **NOT APPROVED – MAJOR AMENDMENT** requested.

19.	REVIEWER:	DATE COMPLETED:	DATE REVISED:
	Eugene L. Schaefer, Ph.D.	2/28/2000	3/6/2000

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information from

CHEMISTRY REVIEW #1

cc: ANDA 40-385
DIV FILE
Field Copy

ES 3/8/2000

Endorsements:

HFD-625/ELSchaefer, Chemist/3-6-00
HFD-625/MSmela, Chemistry Team Leader/3-7-00 MSmela 3/8/00
HFD-617/MDillahunt, Project Manager/3-7-00 MDillahunt 3/8/00

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CHEMISTRY REVIEW - Not APPROVABLE - Major

1. CHEMISTRY REVIEW NO. 2 2. ANDA # **40385**

3. NAME AND ADDRESS OF APPLICANT
Barr Laboratories, Inc.
Attention: Christine Mundkur
2 Quaker Road
PO Box 2900
Pomona, NY 10970-0519

4. LEGAL BASIS FOR SUBMISSION
Approved ANDA Suitability Petition for change in strength

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
——— However, the labeling reviewer informed Barr that the proposed proprietary name is unacceptable. Barr has proposed ———Trexall, and ——— The labeling reviewer has requested a consult from HFD-400.

7. NONPROPRIETARY NAME
Methotrexate Tablets, USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

A1.1 – 1.10 (A1.1 & 1.8 – 1.10 are Chem) (A1.2 – 1.7 are Bio)	07/23/99	Original
A2.1	09/21/99	"Acceptable for Filing" letter
A3.1	10/07/99	Bio telephone amendment
A1.1	03/09/00	NA – Major
"	03/23/00	Fax from Barr re packaging and stability
"	03/28/00	Telecon re 3/23
A4.1 – 4.5	04/14/00	Major amendment
A4.1	08/09/00	Labeling comments to firm via voicemail

In addition to responding to deficiencies, Barr is adding two new strengths, 7.5 mg and 10 mg, and an alternate source of DS, ———

Barr is providing documentation for the manufacture of the new strengths with DS from the same source, ———————————, which was used for making the original exhibit batches of the 5 mg and 15 mg tablets.

Barr has made a new exhibit batch of 15 mg tablets with the ———material, and has put this new batch on the stability program. They are providing comparative dissolution profiles of the 15 mg batches made from the two sources of DS, in the Bio section on pages 06-00033 to 06-00038.

10. PHARMACOLOGICAL CATEGORY
antineoplastic, antirheumatic and antipsoriatic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

Approved ANDA 81-099, Methotrexate Tablets USP, 2.5 mg, Barr Laboratories, Inc.

Bio-IND 15-304, Methotrexate Tablets USP, 15 mg, Barr Laboratories, Inc.

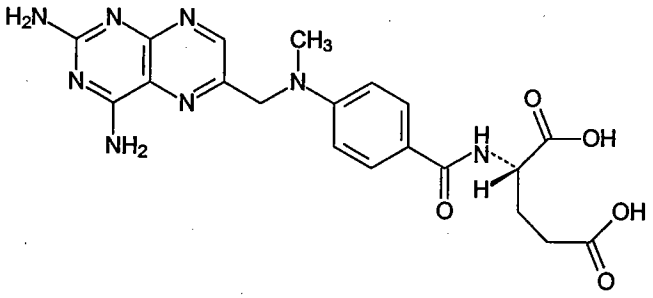
See DMF Checklist.

13. DOSAGE FORM
tablet

14. STRENGTHS 5 mg, 7.5 mg, 10 mg, 15 mg

15. CHEMICAL NAME AND STRUCTURE

Methotrexate. L-Glutamic acid, *N*-[4-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-. $C_{20}H_{22}N_8O_5$. 454.45. 59-05-2.



16. RECORDS AND REPORTS N/A

17. COMMENTS

There are **deficiencies** in the following Review Points:

22, 25, 28.A, 28.B, 29

The conditions of the **other disciplines** are as follows:

25. MANUFACTURING AND PROCESSING (Microbiology)

This is not a sterile product.

31. SAMPLES AND RESULTS

The drug substance and drug product are in USP 24.

32. LABELING

The labeling in the amendment of 4/14/00 was found **not satisfactory** by Ms. Teresa Watkins 5/17/00. Vol. A4.1

33. ESTABLISHMENT INSPECTION

An EER was submitted 9/21/99. The facilities were found acceptable 2/28/2000. However, **a new EER must be submitted to provide for the new drug substance manufacturer** described on page 08-00004 of the amendment of 4/14/00:

34. BIOEQUIVALENCE STATUS

No further questions for 5 mg and 15 mg tablets, 2/16/00.

No further questions for 7.5 mg and 10 mg tablets, 6/1/00.

18. CONCLUSIONS AND RECOMMENDATIONS

ANDA 40-385 is **NOT APPROVED – MINOR AMENDMENT** requested.

19.	REVIEWER:	DATE COMPLETED:	REVISED:
	Eugene L. Schaefer, Ph.D.	10/24/2000	10/27/00

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information from

CHEMISTRY REVIEW #2

1. CHEMISTRY REVIEW NO. 3 2. ANDA # **40385**

3. NAME AND ADDRESS OF APPLICANT
Barr Laboratories, Inc.
Attention: Christine Mundkur
2 Quaker Road
PO Box 2900
Pomona, NY 10970-0519

4. LEGAL BASIS FOR SUBMISSION
Approved ANDA Suitability Petition for change in strengths (4)

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
[redacted] in the original submission was unacceptable. Trexall™ in the minor amendment of 1/12/01 is acceptable.

7. NONPROPRIETARY NAME
Methotrexate Tablets, USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

A1.1 – 1.10 (A1.1 & 1.8 – 1.10 are Chem) (A1.2 – 1.7 are Bio)	07/23/99	Original
A2.1	09/21/99	"Acceptable for Filing" letter
A3.1	10/07/99	Bio telephone amendment
A1.1	03/09/00	NA – Major
"	03/23/00	Fax from Barr re packaging and stability
"	03/28/00	Telecon re 3/23
A4.1 – 4.5 (A4.2 is labeling)	04/14/00	Major amendment
A4.1	08/09/00	Labeling comments to firm via voicemail
"	11/13/00	NA – Minor
A5.1 – 5.3 (5.2 & 5.3 are labeling.)	01/12/01	Minor amendment

Barr added two new strengths, 7.5 mg and 10 mg, and an alternate source of DS, [redacted] in the major amendment of 4/14/00.

10. PHARMACOLOGICAL CATEGORY 11. Rx or OTC
antineoplastic, antirheumatic and antipsoriatic Rx

12. RELATED IND/NDA/DMF(s)

Approved ANDA 81-099, Methotrexate Tablets USP, 2.5 mg, Barr Laboratories, Inc.

Bio-IND 15-304, Methotrexate Tablets USP, 15 mg, Barr Laboratories, Inc.

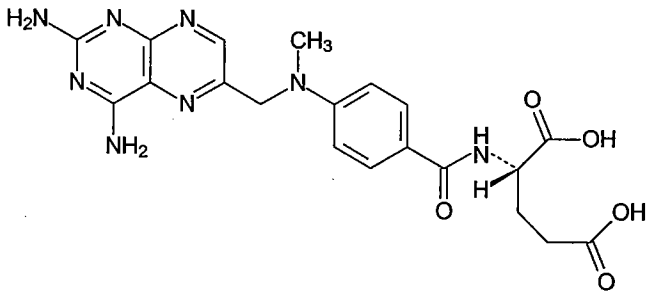
See DMF Checklist.

13. DOSAGE FORM
tablet

14. STRENGTHS 5 mg, 7.5 mg, 10 mg, 15 mg

15. CHEMICAL NAME AND STRUCTURE

Methotrexate. L-Glutamic acid, *N*-[4-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-. $C_{20}H_{22}N_8O_5$. 454.45. 59-05-2.



16. RECORDS AND REPORTS N/A

17. COMMENTS

There are **deficiencies** in the following Review Points:

28.A, 28.B, 29

The conditions of the **other disciplines** are as follows:

25. MANUFACTURING AND PROCESSING (Microbiology)

This is not a sterile product.

31. SAMPLES AND RESULTS

The drug substance and drug product are in USP 24.

32. LABELING

The labeling reviewer is preparing an approval summary, as of 1/31/01.

33. ESTABLISHMENT INSPECTION

The facilities, including [redacted], were found acceptable 10/30/2000.

34. BIOEQUIVALENCE STATUS

No further questions for 5 mg and 15 mg tablets, 2/16/00.

No further questions for 7.5 mg and 10 mg tablets, 6/1/00.

18. CONCLUSIONS AND RECOMMENDATIONS

ANDA 40-385 is **NOT APPROVED – MINOR AMENDMENT** requested.

19. REVIEWER: Eugene L. Schaefer, Ph.D.

DATE COMPLETED: 1/31/01

APPEARS THIS WAY
ON ORIGINAL

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CHEMISTRY REVIEW #3

cc: ANDA 40-385
DUP
DIV FILE
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ES 2/2/01

Endorsements:

HFD-625/ELSchaefer, Chemist/1/31/01
HFD-625/MSmela, Chemistry Team Leader/2/1/01 MSmela 2/5/01
HFD-617/MDillahunt, Project Manager/2/2/01 MDillahunt 2/2/01
F/t by: DJ 2/2/01
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CHEMISTRY REVIEW - Not APPROVABLE - Minor

APPEARS THIS WAY
ON ORIGINAL

1. CHEMISTRY REVIEW NO. 4 2. ANDA # **40385**

3. NAME AND ADDRESS OF APPLICANT
Barr Laboratories, Inc.
Attention: Christine Mundkur
2 Quaker Road
PO Box 2900
Pomona, NY 10970-0519

4. LEGAL BASIS FOR SUBMISSION
Approved ANDA Suitability Petition for change in strengths (4)

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
[redacted] in the original submission was unacceptable. Trexall™ in the minor amendment of 1/12/01 is acceptable.

7. NONPROPRIETARY NAME
Methotrexate Tablets, USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

A1.1 – 1.10 (A1.1 & 1.8 – 1.10 are Chem) (A1.2 – 1.7 are Bio)	07/23/99	Original
A2.1	09/21/99	"Acceptable for Filing" letter
A3.1	10/07/99	Bio telephone amendment
A1.1	03/09/00	NA – Major
"	03/23/00	Fax from Barr re packaging and stability
"	03/28/00	Telecon re 3/23
A4.1 – 4.5 (A4.2 is labeling)	04/14/00	Major amendment
A4.1	08/09/00	Labeling comments to firm via voicemail
"	11/13/00	NA – Minor
A5.1 – 5.3 (5.2 & 5.3 are labeling.)	01/12/01	Minor amendment
A5.1	02/02/01	NC – Labeling
"	02/06/01	NA-Minor
"	02/08/01	Fax from Barr re 02/06/01*
"	02/13/01	Chem telecon re 02/06/01*
"	02/15/01	Minor amendment*
"	02/21/01	Chem telecon re 02/06/01*
"	02/22/01	Minor amendment*

* The subjects of Chemistry Review #4

Barr added two new strengths, 7.5 mg and 10 mg, and an alternate source of DS, ——in the major amendment of 4/14/00. Barr withdrew ——in the minor amendment of 2/22/01.

10. PHARMACOLOGICAL CATEGORY
antineoplastic, antirheumatic and antipsoriatic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

Approved ANDA 81-099, Methotrexate Tablets USP, 2.5 mg, Barr Laboratories, Inc.

Bio-IND 15-304, Methotrexate Tablets USP, 15 mg, Barr Laboratories, Inc.

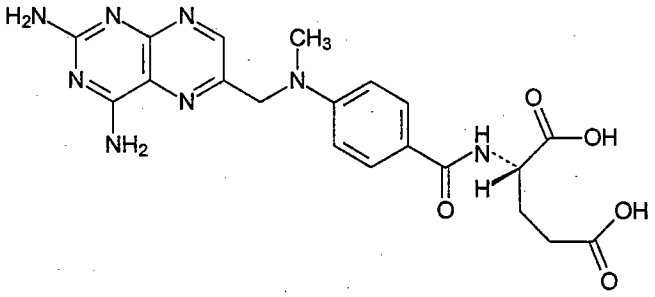
See DMF Checklist.

13. DOSAGE FORM
tablet

14. STRENGTHS 5 mg, 7.5 mg, 10 mg, 15 mg

15. CHEMICAL NAME AND STRUCTURE

Methotrexate. L-Glutamic acid, *N*-[4-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-. $C_{20}H_{22}N_8O_5$. 454.45. 59-05-2.



16. RECORDS AND REPORTS N/A

17. COMMENTS

All chemistry deficiencies have been resolved.

The conditions of the **other disciplines** are as follows:

25. MANUFACTURING AND PROCESSING (Microbiology)

This is not a sterile product.

31. SAMPLES AND RESULTS

The drug substance and drug product are in USP 24.

32. LABELING

The labeling reviewer prepared an approval summary on 2/8/01.

33. ESTABLISHMENT INSPECTION

The facilities were found acceptable 10/30/2000.

34. BIOEQUIVALENCE STATUS

No further questions for 5 mg and 15 mg tablets, 2/16/00.

No further questions for 7.5 mg and 10 mg tablets, 6/1/00.

18. CONCLUSIONS AND RECOMMENDATIONS

ANDA 40-385 can be **APPROVED**.

19. REVIEWER: Eugene L. Schaefer, Ph.D.

DATE COMPLETED: 3/7/01

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information from

CHEMISTRY REVIEW #4

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

None

cc: ANDA 40-385

DIV FILE
Field Copy

Endorsements:

HFD-625/ELSchaefer, Chemist/3/7/01
HFD-625/MSmela, Chemistry Team Leader/3/7/01
HFD-617/MDillahunt, Project Manager/3/8/01
F/T by: DJ 3/8/01
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CHEMISTRY REVIEW - APPROVED

ANDA APPROVAL SUMMARY

ANDA:	CHEMIST:	DATE:
40-385	Eugene L. Schaefer, Ph.D.	3/7/01

DRUG PRODUCT: Methotrexate

FIRM: Barr Laboratories, Inc.

DOSAGE FORM:	STRENGTHS:
Tablets, USP	5 mg, 7.5 mg, 10 mg, 15 mg

cGMP: The facilities were found acceptable on 10/30/00.

BIO: No further questions 2/16/00 and 6/1/00.

VALIDATION - (Description of dosage form received by FDA lab same as in firm's ANDA?): N/A

DS and DP are in USP 24.

STABILITY:

The containers in the stability studies are identical to those in the container section.

LABELING:

Container, carton, and insert labeling were approved by Angela Payne on 2/8/01.

STERILIZATION VALIDATION (If applicable):

N/A

SIZE OF BIO BATCH (Firm's source of NDS ok?): Yes, DMF —— OK.

———— 15-mg tablets

SIZE OF STABILITY BATCHES (If different from bio batch, were they manufactured via the same process?): Yes

5 mg: ———— tablets
7.5 mg: ———— tablets
10 mg: ———— tablets
15 mg: ———— tablets

PROPOSED PRODUCTION BATCHES-MANUFACTURING PROCESS SAME?: Yes

5 mg: ———— tablets
7.5 mg: ———— tablets
10 mg: ———— tablets
15 mg: ———— tablets

Signature of chemist:	Signature of Team Leader:
Eugene L. Schaefer 3/9/01 Eugene L. Schaefer, Ph.D.	Michael Smela for M Smela 3/12/01

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-385

BIOEQUIVALENCE REVIEW(S)

Methotrexate Sodium
15 mg and 5 mg Tablets
ANDA # 40-385
Reviewer: André Jackson

Barr Laboratories
Pomona, N.Y.
Submission Date:
July 23, 1999
October 7, 1999

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Review of A Bioavailability Study on the 15 mg Tablet and Request for Waiver of the 5 mg Tablet and Dissolution Data

RLD: Methotrexate Sodium Tablets 2.5 mg

BACKGROUND:

The firm filed a suitability petition on July 7, 1997 for the submission of 5 mg, 7.5 mg, 10 mg, 12.5 mg and 15 mg methotrexate sodium tablets. The petition was granted and the firm has submitted a study on the 15 mg strength and a request for waiver on the 5 mg strength. The other strengths were withdrawn.

INTRODUCTION:

Methotrexate (formerly Amethopterin) is an antimetabolite used in the treatment of certain neoplastic diseases, severe psoriasis, and adult rheumatoid arthritis.

In adults, oral absorption appears to be dose dependent. Peak serum levels are reached within one to two hours. At doses of 30 mg/m(squared) or less, methotrexate is generally well absorbed with a mean bioavailability of about 60%. The absorption of doses greater than 80 mg/m(squared) is significantly less, possibly due to a saturation effect. Food has been shown to delay absorption and reduce peak concentration.

The terminal half-life reported for methotrexate is approximately three to ten hours for patients receiving treatment for psoriasis, or rheumatoid arthritis or low dose

antineoplastic therapy (less than 30 mg/m(squared)). For patients receiving high doses of methotrexate, the terminal half-life is 8 to 15 hours.

The potential for toxicity from high dose regimens or delayed excretion is reduced by the administration of leucovorin calcium during the final phase of methotrexate plasma elimination. Pharmacokinetic monitoring of methotrexate serum concentrations may help identify those patients at high risk for methotrexate toxicity and aid in proper adjustment of leucovorin dosing.

STUDY OBJECTIVE

The study objective is to determine the bioavailability of a test formulation (Methotrexate Tablets, USP 15 mg, Barr Laboratories, Inc.: 1 x 15 mg) relative to a reference formulation (Methotrexate Sodium Tablets, 2.5 mg, ESI Lederle, Inc.: 6x 2.5 mg) after administration of an equal 15mg single dose to male and female patients with mild to severe psoriasis under fasting conditions.

Fasting Study:

Study Facility Information:

Clinical Facilities:	1. [redacted] 2. 3.
Principal Investigator:	1. [redacted] 2. 3.
Clinical Study Date:	Period I / Period II 1.GRI 10/31/98 / 11/14/98 GRII 1/9/99 / 1/23/99 2.GRI 11/23/98 / 12/7/98 GRII 12/3/98 / 12/17/98 3.GRI 12/2/98 / 12/17/98 GRII 1/8/99 / 1/22/99
Analytical Facility:	[redacted]

Principal Investigator:	[redacted]
Analytical Study Dates:	December 4, 1998-February 22, 1999
Storage Period:	90 days

Study Design:

Protocol No.:	9801 A Single Dose, Fasting Bioequivalence Study Comparing Barr Lab's 15 mg methotrexate sodium 15 mg tablet with 6 x 2.5 mg Lederle methotrexate sodium tablets
Design Type:	Crossover
Randomized:	Y
No. of Sequences:	2
Number of Clinical Sites:	3
Number of Groups/Site:	2
No. of Treatment Periods/Site:	2
No. of Treatments/Site:	2
Washout Period:	14 days
Single, Multiple, Food:	Single

Subjects:

Patients with Mild to Severe Psoriasis:	Y
IRB Approval:	Y
Informed Consent Obtained:	Y
No. of Subjects Enrolled:	38 (22 males,16 females)
Inclusion/Exclusion criteria	vol:1.1 ; pages: 85-87

Special Procedures: Forty-eight hours after methotrexate administration in period II, patients were provided with Leucovorin Calcium tablets (2 x 5 mg) to be taken every 6 hours for four doses(to minimize the risk of myelosuppression).

Housing: Evening prior to each drug administration until 36 hours after dosing on day 2.

Treatment Information:

Treatment:	A	B
Test or Reference:	Test	Reference
Product Name:	Methotrexate sodium	Methotrexate sodium
Strength:	15 mg	2.5 mg
Manufacturer:	Barr Laboratories	ESI Lederle
Batch/Lot No.:	409457R01	457-037
Exhibit Batch Size:	[redacted]	N/A
Expiration Date:	N/A	6/2000
Content Uniformity	95.4%	99.7%
Assay	96.1%	98.7%
Dose Administered:	1 x 15 mg Tablet	6 x 2.5 mg Tablets
Length of Fasting:	10 hr overnight	10 hr overnight

Dosing:

After an overnight fast of ten hours, each subject randomly (Randomization Code in Table 1) received either a test product or a reference product with 240 mL of water. Standard meals were provided at 4 and 10 hours after dosing. Water was not permitted for 1 hour before and 2 hours after dosing in each dosing period.

Table 1. RANDOMIZATION SCHEDULE

Site	Period I	Period II	Subjects
1.GRI	A	B	1,6,7,11
GRII	B	A	2,3,5,9,12,13
2.GRI	A	B	14,15,18,20,23, 24,21,33
GRII	B	A	16,17,19,22,34

3.GRI	A	B	26,27,30,48
GRII	B	A	28,46,67,70

Blood Sampling:

No. of time points	22
Time points	0,0.25,0.5,0.75,1,1.5,2,2.5,3,3.5,4,5,6,7, 8,10,12,16,24,30,36 and 48 hrs

The blood samples were centrifuged and plasma samples were separated and stored at -20°C until analyzed.

The following table gives the formulation for 15 mg Tablet

Ingredient	mg
Core:	
Methotrexate, USP[a]	15
[redacted]	

Coated tablet weight (target)

---

a. Theoretical quantities are based on the Methotrexate, USP assay at 100%.
b. Stated quantity weighed but only partially retained in product after chemical reaction.
c. Dependent on Methotrexate, USP assay.
d. Used but not retained, except as allowed in .
e. Theoretical value based on 3% weight gain.

Analytical Method

The plasma samples were assayed for methotrexate by .

The details of the analytical method for methotrexate are presented in Table 2:

Table 2: Validation data for methotrexate.

Parameter	
Method	
Internal Standard	
Sensitivity/LOQ	
Linearity (Standard curve samples)	
Quality Control (QC) Samples	
Precision of Standards (%CV)	
Precision of QC Samples (%CV)	
Accuracy of Standards (%)	
Accuracy of QC Samples (%)	
Stability	
Freeze-thaw	

Processed Sample Stability at RT	
Long term at -25° C	
Recovery Low Med High	

STATISTICAL ANALYSIS:

AUCL was calculated from zero time to the last non-zero concentration CT. AUCinf, was calculated by extrapolation of AUCL to time infinity by adding CT/K, to AUCL, The elimination rate constant (K) was estimated by linear least squares fitting of the logarithm of the concentrations over the log-linear terminal phase of the concentration versus time profile. Half-life (HL=0.693/K,), maximum concentration attained (Cpeak) and the time of maximum concentration (Tmax) were also calculated. AUCL, AUCI, Cpeak and log transformed AUCL, AUCI and Cpeak was analyzed by Analysis of Variance (ANOVA) with effects for treatments, sequence of dosing, subjects within sequence, study period and study site in the statistical model.

The two one-sided hypotheses at the alpha=0.05 level of significance were tested for AUCL, AUCinf, Cpeak in original scale and after log transformation, by constructing the 90% confidence intervals for the differences between the test and the reference least squares means, and were reported relative to the reference means.

Pharmacokinetics/Statistical Analysis

Results

Of the 38 healthy, adult subjects enrolled in the study, 36 subjects successfully completed both phases of the study. Subject 25 withdrew prior to period 2 dosing. Patient 37 was lost to follow up and the last sample was obtained at the 48

hour time point in period 1.

Table 3. Mean plasma levels of 36 subjects. Values are mean ± sd.

	TEST		REFERENCE	
HOUR0	0.00	0.00	0.41	1.59
HOUR0.25	14.45	18.43	20.21	19.73
HOUR0.5	123.67	89.73	113.04	86.73
HOUR0.75	208.62	101.16	204.26	128.47
HOUR1	265.97	118.74	235.34	128.45
HOUR1.5	296.07	101.39	255.62	106.39
HOUR2	258.33	75.61	248.67	64.52
HOUR2.5	212.93	62.87	233.80	68.23
HOUR3	179.07	49.83	186.60	41.54
HOUR3.5	150.83	41.65	177.58	84.22
HOUR4	119.25	27.58	156.91	73.48
HOUR5	95.21	19.96	105.30	29.30
HOUR6	68.50	13.62	78.42	18.88
HOUR7	52.54	13.27	59.19	15.06
HOUR8	40.89	10.44	48.59	16.26
HOUR10	28.72	9.90	31.90	9.91
HOUR12	16.68	5.36	18.79	6.81
HOUR16	6.79	5.12	7.92	5.17
HOUR24	0.74	1.96	0.82	2.17
HOUR30	0.38	1.47	0.46	1.80
HOUR36	0.36	1.39	0.36	1.41
HOUR48	0.00	0.00	0.00	0.00

Table 4: Mean for test and reference products (N=36). Values are mean ± sd.

	TEST		REFERENCE		RATIO(T/R)
CPEAK ng/mL	347.69	106.37	342.83	79.01	1.01
LCPEAK ng/mL	5.81	0.28	5.81	0.23	1.00[3]
AUCL[1] ng/mL x hr	1235.73	280.24	1310.73	294.18	0.94
LAUCL ng/mL x hr	7.09	0.23	7.16	0.22	0.93

AUCI[2] ng/mL x hr	1282.12	285.52	1358.21	296.46	0.94
LAUCI ng/mL x hr	7.13	0.23	7.19	0.21	0.94
TMAX hr	1.43	0.56	1.69	0.80	---
KEL hr-1	0.23	0.06	0.22	0.05	---
THALF hr	3.29	0.89	3.42	0.91	---

1.AUC 0 to last measured concentration
2.AUC to time infinity
3.Ratio of geometric means

Table 5: 90% CI for pharmacokinetic parameters with site*trt interaction in the model

LCPEAK	93.2-105.9
LAUCL	88.7-97.3
LAUCI	89.3-97.2

ALL CALCULATIONS WERE VERIFIED BY THE REVIEWER

SUBJECTS DID NOT EXHIBIT CPEAK AT THE FIRST NON-ZERO TIME POINT NOR WAS CPEAK OBSERVED AT FIRST MEASURABLE TIME POINT IN THIS STUDY.

Adverse Events

Adverse effects are summarized in Table 3 , vol. 1.2, pages 13-14. The effects were mainly headache and appeared to be equally distributed between test and reference products.

Sample Repeats

Three hundred and eleven out of the one thousand six hundred and twenty-six samples analyzed (19.1%) were reanalyzed. They are listed in volume 1.3, page 62. Most re-analyses were a result of problems with the quality controls.

The following table gives the comparative formulations for the

15 mg and 5 mg Tablets.

Ingredient	15 mg	5mg
Core:		
Methotrexate, USP[a]	15	5

a Theoretical quantities are based on the Methotrexate, USP assay at 100%.
b Stated quantity weighed but only partially retained in product after chemical reaction.

c.Dependent on Methotrexate, USP assay.
d.Used but not retained, except as allowed in [redacted].
e.Theoretical value based on 3% weight gain.

IN-VITRO DISSOLUTION TESTING

The dissolution testing for the test and reference products was conducted using 0.1N HCL as the dissolution media using USP 23 apparatus 2 (Paddle) at 50 rpm. This is a USP method.

Comments:

1. The ANOVA with the interaction term site*trt was significant at the $p<0.1$ level for LAUCL and LAUCI. Therefore the study was analyzed with the site*trt interaction term retained in the model. 90% CI's for this model were within the 80-125% limit.

2.The appended tables for each site shows the reason for the significant site*trt interaction was that site three had higher mean values for LAUC. However since sites 1 and 2 were similar the analysis combining all 3 sites was within the CI limits.

3.The PDR labeling for methotrexate contains the following statement " Food has been shown to delay absorption and reduce peak concentration". However, the Division of Bioequivalence has not required a food effects study for this product for three marketed generic products (ANDA # 81099-Barr ; ANDA # 40-054-Roxanne and ANDA # 81235-Mylan). Two other products reviewed by the Division (ANDA # [redacted] and ANDA # 40-233-Duramed) and not yet approved also did not require food studies. However, there is no information on a possible food effect at the 15 mg dosage level for methotrexate. Two recent references, J.Rheumatol. 1995, April, 22, 630-632 and Arthritis-Rheum. 1992, July, 35, 761-764 (the latter at a dose of 7.5 mg, i.e., 3x2.5 mg tablets) showed no food effects looked at the effects of food on methotrexate. Both studies concluded that there was no food effect which raises additional questions related to the effects of food based upon the statement in the labeling.

4.A survey of PDR labeling for several orally administered anti cancer drugs (list appended to this review) did not report that food had any effect on their absorption. Therefore it appears that the food effect presented in methotrexate labeling may be an exception.

5.The regulatory history of the methotrexate studies reviewed by the Division of Bioequivalence and their status is appended to the review. This data is based upon COMIS. There was no food study requirement for the studies submitted to the Division of Bioequivalence.

RECOMMENDATIONS:

1.The fasting bioavailability study conducted by Barr Laboratories on its 15 mg, methotrexate sodium tablet(lot 409457R01 comparing it to ESI Lederle's methotrexate sodium tablet 6 x 2.5 mg tablets, lot number 457037 has been found to be acceptable to the Division of Bioequivalence. The study demonstrates that Barr Laboratories' 15 mg, methotrexate sodium tablet is bioavailable to 6 x 2.5 mg ESI Lederle's methotrexate sodium tablets.

2.The in vitro dissolution testing conducted on the 15 mg methotrexate sodium tablet has been found to be acceptable.

3. The dissolution testing conducted by Barr on its 5 mg, methotrexate sodium tablet, lot 409277R01 is acceptable. The firm has conducted an acceptable in vivo bioavailabilty study comparing its 15 mg tablet of the test product with 6 x 2.5 mg tablets of the reference product methotrexate sodium manufactured by ESI Lederle. The formulation for the 5 mg strength is proportionally similar to the 15 mg strength of the test product which underwent bioavailability testing. The waiver of the in vivo bioavailibility study requirements for the 5 mg tablet is granted. The 5 mg tablet of the test product is therefore deemed to be bioavailable to 2 x 2.5 mg methotrexate sodium tablets manufactured by ESI Lederle.

4.The dissolution testing should be incorporated into the firm's manufacturing and controls programs. The dissolution testing should be conducted in 900 ml of 0.1N HCL at 37°C using USP XXIII apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

NLT 75% of methotrexate is dissolved in 45 min

André J. Jackson, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHuang
FT INITIALED YCHuang Date 2/8/2000

Concur Date 2/16/00
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

ANDA 40-385 (original, duplicate), HFD 652(Jackson), Drug file, Division File, HFD-650(Division Director).
Appendix, Attachments

Table 6. In Vitro Dissolution Testing

Drug (Generic Name): Methotrexate sodium
Dose Strengths:5 mg and 15 mg
ANDA No.:40-385
Firm: Barr
Submission Date: July 23, 1999
File Name:40385SDW.799

I. Conditions for Dissolution Testing:

USP XXIII Basket: Paddle: x RPM: 50
No. Units Tested: 12
Medium: 0.1N HCL
Wavelength: 306 nm
Volume: 900 mL
Specifications:
NLT 75% in 45 min
Reference Drug: Methotrexate sodium
Assay Methodology: UV Spectroscopy

THIS IS A USP METHOD

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 409277R01 Strength(mg) 5			Reference Product Lot # 457-037 Strength(mg) 2.5		
	Mean	Range	%CV	Mean	Range	%CV
10	87	77-92	6.3	52	49-56	4.7
20	88	80-93	5.2	97	94-100	2.2
30	89	82-93	4.5	99	96-104	2.8
45	91	84-94	4.2	100	97-105	2.9
75	92	87-95	3.2	99	96-104	2.6
Sampling Times (Minutes)	Test Product Lot # 409457R01 Strength(mg) 15			Reference Product Lot # 457-037 Strength(mg) 2.5		
	Mean	Range	%CV	Mean	Range	%CV
10	89	76-95	7.2	52	49-56	4.7
20	91	81-95	5.0	97	94-100	2.2
30	92	83-96	4.4	99	96-104	2.8
45	92	84-95	3.8	100	97-105	2.9
75	93	85-96	3.5	99	96-104	2.6

APPENDIX

Site 1

Variable	N	Mean TEST	Std	Mean REFERENCE	Std	Ratio (TEST/REFERENCE)
CPEAK ng/mL	15	335.53	103.80	331.27	82.72	
LCPEAK ng/mL	15	5.77	0.31	5.77	0.26	1.0
AUCL ng/mL x hr	15	1229.71	241.65	1305.83	227.08	
LAUCL ng/mL x hr	15	7.09	0.21	7.16	0.18	0.93
AUCI ng/mL x hr	15	1274.51	246.81	1347.00	223.56	
LAUCI ng/mL x hr	15	7.13	0.21	7.19	0.17	0.94
TMAX hr	15	1.34	0.43	1.98	0.91	
KEL hr-1	15	0.21	0.05	0.23	0.05	
THALF hr	15	3.42	0.87	3.24	0.83	

Site 2

Variable	N	Mean TEST	Std	Mean REFERENCE	Std	Ratio (TEST/REFERENCE)
CPEAK ng/mL	13	365.54	132.97	345.46	89.33	
LCPEAK ng/mL	13	5.85	0.31	5.82	0.25	1.03
AUCL ng/mL x hr	13	1194.19	267.17	1179.85	244.33	
LAUCL ng/mL x hr	13	7.06	0.23	7.05	0.21	1.01
AUCI ng/mL x hr	13	1235.75	261.60	1231.02	246.61	
LAUCI ng/mL x hr	13	7.10	0.22	7.10	0.20	1.00
TMAX hr	13	1.44	0.66	1.16	0.36	
KEL hr-1	13	0.24	0.06	0.20	0.05	
THALF hr	13	2.98	0.64	3.63	1.07	

Site 3

Variable	N	Mean	Std	Mean	Std	Ratio (TEST/REFERENCE)
CPEAK ng/mL	8	341.50	61.30	360.25	56.57	
LCPEAK ng/mL	8	5.82	0.18	5.88	0.15	0.94
AUCL ng/mL x hr	8	1314.51	378.35	1532.59	372.99	
LAUCL ng/mL x hr	8	7.15	0.29	7.31	0.22	0.85
AUCI ng/mL x hr	8	1371.73	393.90	1585.91	381.64	
LAUCI ng/mL x hr	8	7.19	0.29	7.35	0.22	0.85
TMAX hr	8	1.56	0.62	2.00	0.71	
KEL hr-1	8	0.22	0.07	0.21	0.05	
THALF hr	8	3.53	1.21	3.42	0.79	

CC: ANDA 40385
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Draft and Final with Dates)
HFD-652/Reviewer
HFD-652/Bio Team Leader
HFD-617/Project Manager
HFD-650/Dale Conner 2/16/00

V:\Firmsam\Barr\Ltr&Rev\40385SDW.799

BIOAVAILABILITY - ACCEPTABLE Submission Date: July 23, 1999

1. **FASTING STUDY** (STF) o/c Strength: 15 mg Tablet _____

Clinical: 1. [redacted]
2.
3.

Analytical: [redacted]

Outcome: AC

2. **Dissolution WAIVER** (DIW) Strength: 5 mg Tablet
o/c **Outcome: AC**

Submission Date: October 7, 1999

3. **STUDY AMENDMENT** (STA) Strength: 15 mg _____
Disk and Additional
Information **Outcome: AC**

3.1
Gene Sharpe

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA 40-385 APPLICANT: Barr Laboratories

DRUG PRODUCT: Methotrexate 15 mg and 5 mg Tablets

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

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 24.

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,

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

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 40-385 SPONSOR : Barr Laboratories

DRUG AND DOSAGE FORM : Methotrexate Sodium Tablets

STRENGTH(S) : **15 mg and 5 mg**
TYPES OF STUDIES : Single Dose

CLINICAL STUDY SITE(S) :1.
2.
3.

ANALYTICAL SITE(S) :

STUDY SUMMARY : See Review

DISSOLUTION : See Submission

DSI INSPECTION STATUS

Inspection needed: YES / NO	Inspection status:	Inspection results:
First Generic ___	Inspection requested: (date)	
New facility X	Inspection completed: (date)	
For cause ___		
Other ___		

PRIMARY REVIEWER : Andre Jackson BRANCH : I

INITIAL : _____ DATE : 2/9/2000

TEAM LEADER : Y.C. Huang BRANCH : I

INITIAL : _____ DATE : 2/9/2000

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : _____ DATE : 2/16/00

4.1 Smelter

Methotrexate Sodium
15 mg, 10mg, 7.5mg
and 5 mg Tablets
ANDA # 40-385

Barr Laboratories
Pomona, N.Y.
Submission Date:
April 14, 2000

Reviewer: André Jackson
V:\Firmsam\Barr\Ltr&Rev\40385A.400

Review of A Study Amendment for the 15 mg Bioequivalence Study: A Request for Dissolution Waiver for 10 mg and 7.5 mg Tablets

RLD: Methotrexate Sodium Tablets 2.5 mg

BACKGROUND:

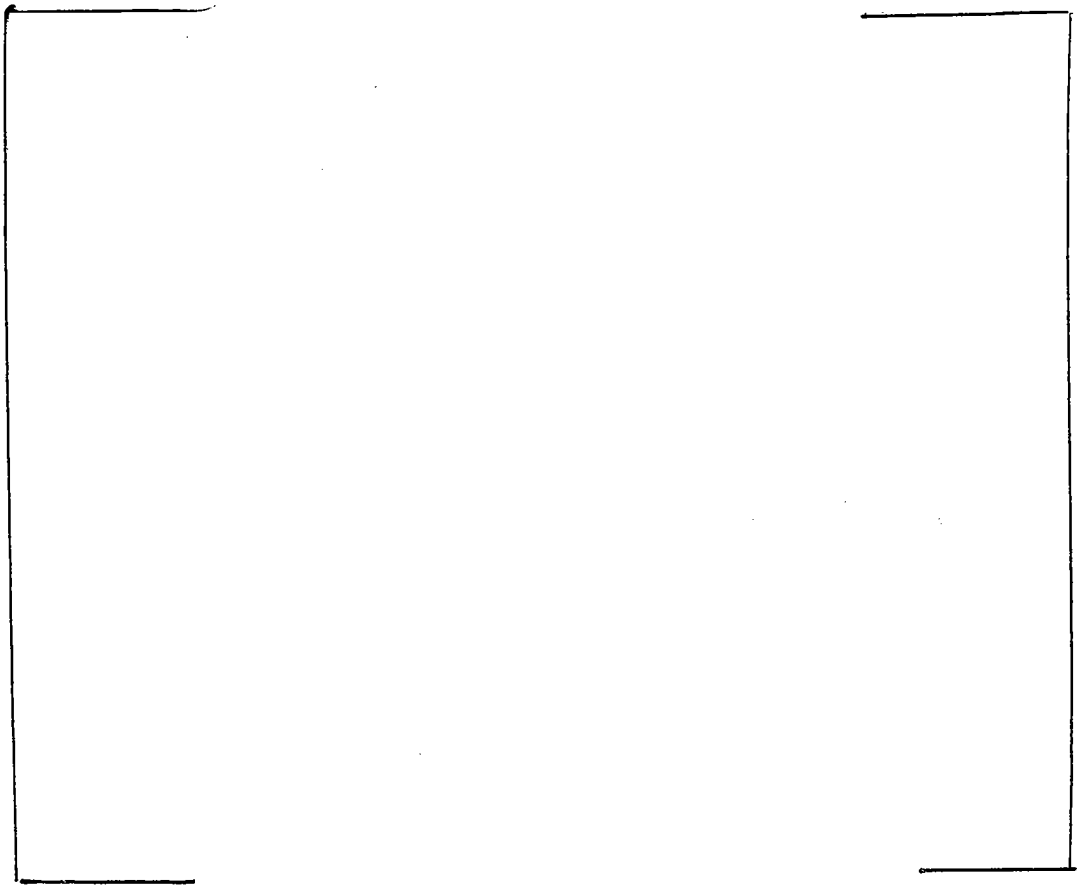
The firm filed a suitability petition on July 7, 1997 for the submission of 5 mg, 7.5 mg, 10 mg, 12.5 mg and 15 mg methotrexate sodium tablets. The petition was granted and the firm has submitted a study on the 15 mg strength and a request for waiver on the 5 mg strength. The other strengths were withdrawn. The 15 mg study was reviewed and found to be acceptable by the Division of Bioequivalence but the approval is pending in OGD. Barr has submitted the current request for waiver for 10 mg and 7.5 mg tablets based upon the submitted 15 mg study. In addition, Barr is also submitting documentation to provide for an alternate source of drug substance. In accordance with FDA Policy and Procedure Guide #22-90, "Interim Policy on Exemptions to the Batch-Size and Production Condition Requirements for Non-Antibiotic, Solid Oral-Dosage Form Drug Products Supporting Proposed ANDAs" (9/13/90). Barr made one batch of the 15 mg strength (bioequivalency batch strength) with the ——— material and placed it into its stability program (controlled room temperature and accelerated conditions). In addition, a dissolution profile was generated comparing the enclosed ——— material test batch with Barr's ——————— material bioequivalency batch.

Formulation data

The following table compares the formulation (mg/dose) of Methotrexate Tablets, USP 7.5 mg, 10

mg with that of the 5 mg and 15 mg (bioequivalence) strengths submitted in the original application.

Ingredient	5 mg	7.5 mg	10 Mg	15 mg
Core:				
Methotrexate, USP[(a)]	5	7.5	10	15



Comments:

1. The active and inactive ingredients and their concentrations for the 10 mg and 7.5 mg tablets are compositionally proportional to the 15 mg tablet which underwent a bioequivalence study.

2. Pursuant to 21 CFR 320.22(d)(2) the request for waiver of the in vivo bioequivalence requirements for the 10 mg and 7.5 mg tablets may be granted based upon the final approval of the 15 mg bioequivalence study by OGD.

3. The f2 values for the dosage strengths were estimated to be:

Tablet Strength	vs Reference Strength	Tablet Strength	vs Test 15 mg Strength
15 mg	35.23	10 mg	70.9

10 mg	40.83	7.5 mg	62.1
7.5 mg	39.61	-----	
5 mg	35.36	-----	

These values were calculated using the mean data since the per cent coefficients of variation for the earlier time points were less than 20% and other time points were also less than 10%. The F2 values versus the same strength reference are below 50. However, the F2 values using the test product 15 mg tablet (i.e., biostudy strength) as the reference are above 50. In both cases, the F2 values are not problematic since 90% dissolution is achieved within 20 min.

4. The firm submitted dissolution data comparing the 10 mg strength with 4x2.5 mg tablets of the reference and the 7.5 mg strength compared to 3x2.5 mg reference tablets. The results were similar to those versus 1 tablet of reference.

5. The dissolution data submitted for the 15 mg tablet manufactured from the alternate source, ———, is comparable to that from the original source ———.

RECOMMENDATIONS:

1. The dissolution testing conducted by Barr on its 10 mg methotrexate sodium tablet, lot 409299R01 and its 7.5 mg, methotrexate sodium tablet, lot 409289R01 and is acceptable. The firm has conducted an acceptable in vivo bioavailabilty study comparing its 15 mg tablet of the test product with 6 x 2.5 mg tablets of the reference product methotrexate sodium manufactured by ESI Lederle. The formulations for the 10 mg and 7.5 mg strengths are proportionally similar to the 15 mg strength of the test product which underwent bioavailability testing. The waiver of the in vivo bioavailibility study requirements for the 10 mg and 7.5 mg tablet is granted pending approval of the 15 mg study by OGD.

2. The dissolution testing for the 15 mg tablet lot # 409459R01 of the test Barr product manufactured with the ——— drug substance comparing it to the 15 mg tablet lot #

409457R01 of the Barr product manufactured with the ——— drug substance and used in the bioequivalence study is acceptable. The waiver of the in vivo bioavailibility study requirements for the Barr methotrexate 15 mg tablet product manufactured with the ——— drug substance is granted pending approval of the 15 mg study by OGD.

2.The dissolution testing should be incorporated into the firm's manufacturing and controls programs. The dissolution testing should be conducted in 900 ml of 0.1N HCL at 37°C using USP XXIV apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

NLT 75% of methotrexate is dissolved in 45 min

André J. Jackson, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHuang
FT INITIALED YCHuang

Date 5/23/2000

Concur:

Date 6/1/00

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

ANDA 40-385 (original, duplicate), HFD 652(Jackson), Drug file, Division File, HFD-650(Division Director).

Dissolution Conditions:

USP XX~~III~~ IV Basket: Paddle: x RPM: 50
No. Units Tested: 12
Medium: 0.1N HCL
Wavelength: 306 nm
Volume: 900 mL
Specifications:
NLT 75% in 45 min
Reference Drug: Methotrexate sodium
Assay Methodology: UV Spectroscopy
THIS IS A USP METHOD

IN-Vitro COMPARATIVE DISSOLUTION STUDY

Sampling Times (Minutes)	Test Product Lot # 409289R01 Strength 7.5 mg					Reference Product Lot # 457-037 Strength 2.5 mg					
	% Dissolved					% Dissolved					
Sample No.	10 min.	20 min.	30 min.	45 min.	75* min.	Sample No.	10 min.	20 min.	30 min.	45 min.	75* min.
1						1					
2						2					
3						3					
4						4					
5						5					
6						1					
7						7					
8						8					
9						9					
10						10					
11						11					
12						12					
Mean	89	92	94	95	96	Mean	57	94	95	93	94
Max	95	98	99	100	101	Max.	60	101	98	98	100
Min.	81	86	88	90	91	Min.	53	90	91	75	8 3
%RSD.	4.6	4	3.7	3.3	3	%RSD.	4.8	2.9	2.2	6.8	5

*Additional time point at the same rotation speed.

IN-Vitro COMPARATIVE DISSOLUTION STUDY

Sampling Times (Minutes)	Test Product Lot # 409299R01 Strength 10 mg					Reference Product Lot # 457-037 Strength 2.5 mg					
	% Dissolved						% Dissolved				
Sample No.	10 min	20 mm.	30 min.	45 min.	75* min.	Sample No.	10 min.	20 min.	30 min.	45 min.	75* min
1						1					
2						2					
3						3					
4						4					
5						5					
6						6					
7						7					
8						8					
9						9					
10						10					
11						11					
12						12					
Mean	87	90	92	93	95	Mean	57	94	95	93	94
Max.	93	96	97	98	99	Max.	60	101	98	98	100
Min.	78	84	86	88	90	Min.	53	90	91	75	83
%RSD.	5.9	4.6	3.9	3.7	3.2	%RSD.	4.8	2.9	2.2	6.8	5

*Additional time point at the same rotation speed.

Sampling Times (Minutes)	Test Product Lot # 409459R01 Strength 15 mg					Reference Product Lot # 409457R01 Strength 15 mg					
	% Dissolved						% Dissolved				
Sample No.	10 min.	20 min.	30 min.	45 min.	75* min.	Sample No.	10 min.	20 min.	30 min.	45 min.	75* min.
1						1					
2						2					
3						3					
4						4					
5						5					
6						1					
7						7					
8						8					
9						9					
10						10					
11						11					
12						12					
Mean	92	94	95	96	96	Mean	83	88	89	90	91
Max	94	95	96	97	97	Max.	95	96	96	96	96
Min.	85	93	94	94	95	Min.	69	80	82	83	8 5
%RSD.	2.5	0.8	0.8	0.9	0.8	%RSD.	10.1	5.6	5.0	4.4	3.7

APPEARS THIS WAY

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA 40-385 APPLICANT: Barr Laboratories

DRUG PRODUCT: Methotrexate 15mg, 10mg, 7.5mg and 5.0mg Tablets

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

However, the waiver can not be granted until the 15 mg tablet has been approved.

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 24.

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,

Dale P. Conner

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

#2

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 40-385 SPONSOR :Barr Laboratories, Inc.

DRUG AND DOSAGE FORM : Methotrexate Sodium Tablets

STRENGTH(S) : 15mg, 10 mg, 7.5 mg and 5.0 mg

TYPES OF STUDIES : Single Dose BA study on 15 mg / waiver on 10 mg 7.5mg and 5 mg.

CLINICAL STUDY SITE(S) :1. [redacted]
2. [redacted]
3. [redacted]

ANALYTICAL SITE(S) : [redacted]

STUDY SUMMARY : See Review(Approval was pending DSI inspection completed on (9/29/2000)

DISSOLUTION : See Submission

DSI : Acceptable YH

DSI INSPECTION STATUS

Inspection needed: YES / NO	Inspection status:	Inspection results:
First Generic ____	Inspection requested: (date)	
New facility ____	Inspection completed: (date)	
For cause ____		
Other ____		

PRIMARY REVIEWER : Andre Jackson BRANCH : I

INITIAL : AJ DATE : 12/4/2000

TEAM LEADER : Y.C. Huang BRANCH : I

INITIAL : YH DATE : 12/4/2000

for DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : Barbara McCall DATE : 12/8/00

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-385

ADMINISTRATIVE DOCUMENTS

a request for

EDL 3/6/01

RECORD OF TELEPHONE CONVERSATION

Barr Laboratories received a minor amendment on 2/6/01. The firm submitted a fax to the Agency to request a telecon to discuss comment 2 of the deficiency letter. (see attached fax).

Mike Smela reviewed the fax and I telephoned the firm and left the following voice mail message for Mr. Sharif Ahmed: It is policy to require full term data if accelerated show adverse trends.

DATE
February 13, 2001

ANDA NUMBER
40-385

IND NUMBER

TELECON

INITIATED BY

SPONSOR X

FDA

PRODUCT NAME
Methotrexate Tablets USP

FIRM NAME
Barr Laboratories

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Sharif Ahmed

TELEPHONE NUMBER
(913) 353-8476

SIGNATURE

M.Dillahunt

M Dillahunt 2/13/01

V:\FIRMSAM\BARR\TELECONS\40385tcon.4.doc

CC: ANDA 40-385
Chem Div I, T-con Notebook

a request for

ESS

3/6/01

RECORD OF TELEPHONE CONVERSATION

Barr Laboratories received a minor amendment on 2/6/01. The firm submitted a fax to the Agency to request a telecon to discuss comment 2 of the deficiency letter. (see attached fax) even though they already have submitted a response.

Ms. Christine Mundkur of Barr Laboratories stated she needed clarification regarding comment#2. Ms. Mundkur stated there was no trending down in CRT for the 5 mg and 15 mg of the original batches. Ms. Mundkur felt this data could be used to support stability for the 7.5 mg, 10 mg and 15 mg strengths of the alternate vendor.
Mr. Smela informed her the Agency does not allow generic firms to matrix strengths at this time.
Mr. Smela stated that it is policy to require full term data if accelerated data show adverse trends.

Mr. Smela stated that the firm had the option of reducing their expiration date, and or/withdrawing the alternate supplier.

The firm questioned what is meant by adverse trend.
Mr. Smela stated ICH has a definition for significant change in the stability guidance, however it is currently not implemented in OGD and a significant change is defined on a case by case basis.

Mr. Smela also informed the firm the chemistry reviewer is on leave for 2 weeks. If there is no additional information submitted to their application regarding comment 2, the firm will likley receive another not approvable letter.

Ms. Mundkur stated the firm will amend the ANDA before 2 weeks.

DATE
February 21, 2001

ANDA NUMBER
40-385

IND NUMBER

TELECON

INITIATED BY

SPONSOR X

FDA

PRODUCT NAME
Methotrexate Tablets USP

FIRM NAME
Barr Laboratories

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Sharif Ahmed
Christine Mundkur

TELEPHONE NUMBER
(913) 353-8476

SIGNATURE

M.Smela M.Smela 2/21/01
M.Dillahunt 2/21/01

V:\FIRMSAM\BARR\TELECONS\40385tcon.5.doc
CC: ANDA 40-385
Chem Div I, T-con Notebook

2-21-01 / Tel / Telecon

RECORD OF TELEPHONE CONVERSATION

The firm received a major amendment on 3/9/2000. The firm submitted a fax to the Agency on 3/23/2000 requesting a telecon to discuss chemistry comment #14. (see attached fax)

Please provide stability data for both tablet strengths packaged in the actual container sizes, 30's and 60's, and using the same closure, CRC, that will be used for marketing. It is not acceptable to bracket stability studies using presentations that are not proposed in the ANDA nor intended market.

Mike Smela informed the firm the stability data pre and post approval should include the smallest and largest container/closure proposed for marketing. The firm can bracket container/closures as long as they are the same, except for size including closures and liners.
Mr. Smela also informed the firm that their post approval stability protocol must be consistent with any changes made in the ANDA. Labeling is also needed for all container/ closures.

The firm had a question about the tradename they propose to use for their product.
Mr. Smela referred the firm to contact John Grace for questions about the tradename.

DATE
March 28, 2000

ANDA NUMBER
40-385

IND NUMBER

TELECON

INITIATED BY

X **SPONSOR**

FDA

PRODUCT NAME
Methotrexate Tablets 5mg and 15 mg

FIRM NAME
Barr Laboratories

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Christine Mundker
Sharif Ahmed

TELEPHONE NUMBER
(914) 353-8432

SIGNATURE
M.Dillahunt 5/25/00
M.Smela

V:\FIRMSAM\BARR\TELECONS\40385.tcon3.doc

CC: ANDA 40-385
Division File
Chem Div I, T-con Notebook

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-385

CORRESPONDENCE

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

July 23, 1999

505(b)(2)(A) OK
9/21/99

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

REFERENCE: ABBREVIATED NEW DRUG APPLICATION
METHOTREXATE TABLETS, USP
5 MG AND 15 MG

In accordance with the regulations promulgated under 505 (j) of the Food, Drug and Cosmetic Act, and as amended, Barr Laboratories, Inc. is submitting this Abbreviated New Drug Application for Methotrexate Tablets, USP 5 mg and 15 mg.

On June 24, 1999, the Office of Generic Drugs refused to file Barr's ANDA 40-370 for Methotrexate Tablets, USP 5 mg, 7.5 mg, 10 mg and 15 mg on the ground that one batch of each strength were not made with the primary source of drug substance. At this time, Barr is submitting this application for Methotrexate Tablets, USP 5 mg and 15 mg, containing supporting data from one batch of each strength manufactured with a single source of drug substance.

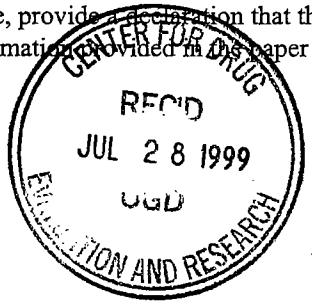
Barr's Abbreviated New Drug Application for Methotrexate Tablets, USP 5 mg and 15 mg is based on a suitability petition, Docket No 97P-0279/CP1, filed by Pitney, Hardin, Kipp & Szuch for Methotrexate Sodium Tablets, 5 mg, 7.5 mg, 10 mg, 12.5 mg and 15 mg (base) and approved by the Agency on August 22, 1997.

The application is provided in duplicate, as an archival copy, and a review copy. The archival copy of the application is contained in blue binders and consists of 10 volumes. The chemistry, manufacturing and controls part of the review copy is contained in red binders and consists of 4 volumes. The bioequivalence part of the review copy is contained in orange binders and consists of 7 volumes.

Included in this application and in accordance with the Generic Drug Enforcement Act of 1992, are Debarment Certification Statements from Barr and outside contractors. A Field Copy of this application has been forwarded to the Maryland District Office. A Field Copy Certification is also provided in this application.

Certifications of financial interests and arrangements of clinical investigators conducting the bioequivalence study are provided in Section VI.

The CMC section of this application will be provided in electronic format within 30 days from this date. Barr Laboratories, Inc. will, at that time, provide a declaration that the information in the electronic submission is the same as the information provided in the paper submission.



METHOTREXATE TABLETS, USP
5 MG AND 15 MG

The format of this application is in accordance with Office of Generic Drug's Guidance for Industry: Organization of an ANDA, dated February 1999. The information submitted in this application is also in accordance with the October 14, 1994 communication from Dr. Janet Woodcock, (CDER) and Mr. Ronald Chesemore (ORA).

If you have any questions concerning this application, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859. Your earliest acknowledgment to this application will be very much appreciated.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality
and Regulatory Counsel

mub

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

August 6, 1999

NEW CORRESP

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

40-385

RW

REFERENCE: METHOTREXATE TABLETS, USP
5 MG AND 15 MG
AMENDMENT: CMC ELECTRONIC SUBMISSION

Reference is made to our Abbreviated New Drug Application submitted July 23, 1999 under 505(j) of the Food, Drug and Cosmetic Act for Methotrexate Tablets, USP 5 mg and 15 mg.

As indicated in our original application, Barr Laboratories, Inc. is amending the above referenced application to provide the CMC electronic submission. The CMC electronic submission is contained on a single diskette labeled "ESD & Companion Document". A backup diskette containing identical information is also provided. The ESD file is named "Brl9901.003" and the MicroSoft Word Companion Document file is named "Brl9901.004".

Barr Laboratories, Inc. declares that the information provided in the electronic submission is the same as the information provided in the paper submission.

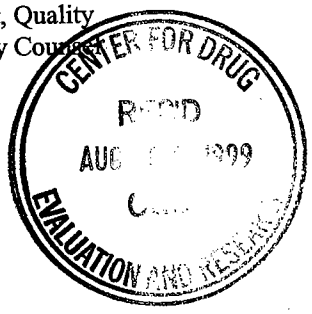
A copy of this letter has been forwarded to the Baltimore District Office.

If you have any questions concerning this application, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859. Your earliest acknowledgment to this application will be very much appreciated.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality
and Regulatory Co[illegible]



Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

September 20, 1999

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

NEW CORRESP
NC

REFERENCE: ANDA 40-385
METHOTREXATE TABLETS, USP
5 MG AND 15 MG
GENERAL CORRESPONDENCE

Reference is made to our Abbreviated New Drug Application 40-385 for Methotrexate Tablets, USP 5 mg and 15 mg, submitted on July 23, 1999. Reference is also made to the September 8, 1999 discussion with Lt. Gregory Davis of the Office of Generic Drugs.

As requested by the Agency, following is a list of sites used in conducting the bioequivalence study for Methotrexate Tablets, 15 mg.

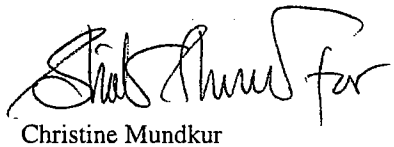
	Facilities	**Function**
1.	[redacted]	Clinical Site
2.		Clinical Site
3.		Clinical Site
4.		Clinical Site
5.		Laboratory for Screening and Safety Tests
6.		Laboratory for Screening and Safety Tests

	Facilities	Function
7.	[redacted]	Laboratory for Screening and Safety Tests
8.		Laboratory for Screening and Safety Tests
9.		Bio-analytical method development and validation, bio-analytical testing and statistical analysis

If you have any questions concerning this correspondence, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely,

BARR LABORATORIES, INC.



Christine Mundkur
Vice President, Quality
and Regulatory Counsel

2.1

ANDA 40-385

Barr Laboratories, Inc.
Attention: Christine Mundkur
2 Quaker Road
P.O. Box 2900
Pomona, NY 10970

SEP 21 1999

Dear Madam:

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

Reference is made to the telephone conversation dated September 8, 1999 and your correspondence dated September 20, 1999.

NAME OF DRUG: Methotrexate Tablets USP, 5 mg and 15 mg

DATE OF APPLICATION: July 23, 1999

DATE (RECEIVED) ACCEPTABLE FOR FILING: July 28, 1999

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:

Michelle Dillahunt
Project Manager
(301) 827-5848

Sincerely yours,

for

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 40-385
cc: DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-92
HFD-615/M.Bennett
Endorsement:
HFD-615/NMahmud, Chief, RSB _____ date 9/21/99
HFD-615, GDavis, CSO _____ date 9/21/99
HFD-600, MSmela, Sup. Chem. _____ date
Word File v:\firmsam\barr\ltrs&rev\40385.ack
FT\njg\9\21\99
ANDA Acknowledgment Letter!

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773
Attn: Elaine Hu

October 7, 1999

NDA DRUG AMENDMENT
AB

REFERENCE: ANDA 40-385
METHOTREXATE TABLETS, USP
5 MG AND 15 MG
TELEPHONE BIOEQUIVALENCE AMENDMENT

Reference is made to our Abbreviated New Drug Application 40-385 for Methotrexate Tablets, USP 5 mg and 15 mg, submitted on July 23, 1999. Reference is also made to the September 23, 1999 discussion with Elaine Hu of the Office of Generic Drugs.

As requested by the Agency, Barr is providing a revised diskette and a backup copy that contain the two additional fields for the study sites and groups to the tables containing the pharmacokinetic data and are provided in Attachment 1. Comprehensive lists of clinical sites and their function related to the bioequivalence study for Methotrexate Tablets, 15 mg have also been clarified and are provided in Attachment 2.

If you have any questions concerning this correspondence, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality
and Regulatory Counsel

CENTER FOR DRUG
RECD
OCT 12 1999

MAJOR AMENDMENT

ANDA 40-385

MAR 9 2000

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)

TO: APPLICANT: Barr Laboratories, Inc. PHONE: (914) 362-1100

ATTN: Christine Mundkur FAX: (914) 353-3859

FROM: Michelle Dillahunt PROJECT MANAGER (301) 827–5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated July 23, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Methotrexate Tablets USP, 5 mg and 15 mg .

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (4 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 MAJOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MAJOR 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 this represents a second or greater occasion upon which significant (MAJOR) deficiencies have been identified, please contact the Project Manager within 30 days for further clarification or assistance.

SPECIAL INSTRUCTIONS:

CMC and Labeling Comments Included

X:\new\ogdadmin\macros\faxmaj.frm

5/9/00

Redacted 3 page(s)

of trade secret and/or

confidential commercial

information from

3/9/2000 FDA FAX

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

ANDA Number: 40-385 **Date of Submission: July 23, 1999**
Applicant's Name: Barr Laboratories, Inc.
Established Name: Methotrexate Tablets USP, 5 mg and 15 mg
Proposed Proprietary Name: ———
Labeling Deficiencies:

1. GENERAL COMMENTS – Your proposed proprietary name has been found unacceptable based on 21 CFR 201.10(c)(5). It sounds like or looks like the following proprietary names already on the market: ———— . Please remove it from all labels and labeling.

2. CONTAINER (30's and 60's)

   i. Caution- Revise the second and third sentences in this section to read as follows:

   Prescriptions should not be written or refilled on a PRN basis. Refill of prescriptions should be by direct order (written or oral) of the physician only. See Boxed Warnings for complete directions for use.

   ii. Include the statement "KEEP OUT OF REACH OF CHILDREN."

3. UNIT DOSE BLISTER (1's)- See comment under GENERAL COMMENTS.

4. UNIT DOSE BLISTER CARTON (1 x 5 mg, and ———— - See comments under GENERAL COMMENTS and (ii) under CONTAINER.

5. PROFESSIONAL SAMPLE DISPENSER (10 x 1[5 mg] and ———— - See comments under GENERAL COMMENTS and (ii) under CONTAINER.
6. INSERT
   a. Revise your insert to be in accord with the most recent labeling for the reference listed drug, Methotrexate Tablets USP (Lederle; NDA# 08-085/S0048; approved October 29, 1999). The labeling may be obtained from Freedom of Information or the following website – http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html.
   b. See comment under GENERAL COMMENTS.

Please revise your labels and labeling, as instructed above, and submit 4 copies of draft labels and labeling. We will not request final print labels and labeling until a determination has been made regarding the acceptability of your proposed proprietary name.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes- http://www.fda.gov/cder/ogd/rld/labeling_review_branch.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 the reference listed drug labeling with all differences annotated and explained.

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

barr Laboratories, Inc.

2 Quaker Road
P.O. Box 2900
Pomona, NY 10970
914-362-1100

Fax Transmission

Date: March 23, 2000

To: Michelle Dilahunt
Project Manager, OGD

Phone Number: (301) 827-5848
Fax Number: (301) 594 -0180

From: Sharif Ahmed
Manager of Regulatory Affairs
Barr Laboratories, Inc.

Phone Number: (913) 353-8476
Fax Number: (914) 353-3859

Pages 1

Message:

Reference is made to our ANDA 40-385 for Methotrexate Tablets, USP 5 mg and 15 mg submitted on July 23, 1999. Reference is also made to a Major Amendment dated March 9, 2000. We are sending this facsimile to request a discussion with the review branch concerning comment 14.

In view of a recent partnership agreement with DuPont Pharmaceuticals, Barr has revised its marketing strategy for Methotrexate Tablets, 5 mg and 15 mg. Once approved, DuPont will market Methotrexate Tablets, 5 mg and 15 mg. According to this arrangement, Barr would like to manufacture Methotrexate Tablets, 5 mg and 15 mg in containers of 4, 30, 60 and 100 tablets [redacted] containers of 4 tablets [redacted] will be used as professional samples. The containers of 30, 60 and 100 tablets will be sold in the market. Therefore, Barr would be seeking approval for the Methotrexate Tablets, 5 mg and 15 mg in containers of 4, 30, 60 and 100 tablets [redacted]

The submission batches of Methotrexate Tablets, USP 5 mg and 15 mg were packaged in containers of 4 tablets and 100 tablets. The same container closure system was used for the packaging of these two configurations. The stability data generated for these packaging configurations brackets the packaging configurations proposed for commercial production.

Since Barr would now be seeking approval for all of the above mentioned package sizes, we believe this meets requirements for submission of stability data. However, we would like to confirm if this addresses the reviewer's concern expressed in comment 14. We will appreciate if you would arrange a teleconference with the review branch.

Verification Name/Number: _____

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

April 14, 2000

ORIG AMENDMENT
N/Ac

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

REFERENCE: **ANDA 40-385**
Methotrexate Tablets, USP 5 mg and 15 mg
Additional Strengths: Methotrexate Tablets, USP 7.5 mg and 10 mg
MAJOR AMEDMENT

Reference is made to our Abbreviated New Drug Application 40-385, submitted on July 23, 1999, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Methotrexate Tablets, USP 5 mg and 15 mg. Reference is also made to your facsimile dated March 9, 2000. The deficiencies identified in the facsimile and our responses are as follows:

CHEMISTRY DEFICIENCIES

A. Deficiencies

COMMENT 1:

[redacted]

RESPONSE:

[redacted]

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information from

4/14/2000 BARR LETTER

COMMENT

Please revise your labels and labeling, as instructed above, and submit 4 copies of draft labels and labeling. We will not request final print labels and labeling until determination has been made regarding the acceptability of your proposed proprietary name.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes- http:/www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.04 (a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained.

RESPONSE:

As requested by the Agency, Barr is providing 4 copies of draft labeling in Section V. To facilitate review, and in accordance with 21 CFR 314.04 (a)(8)(iv), side-by-side comparisons of our proposed labeling with the previously submitted labeling are provided in Section IV.

The CMC and Bioequivalence section of this application will be provided in electronic format within 30 days from this date. Barr Laboratories, Inc. will, at that time, provide a declaration that the information in the electronic submission is the same as the information provided in the paper submission.

A Field Copy of this application has been forwarded to the Baltimore and Philadelphia District Offices.. A Field Copy Certification is also provided.

This completes the present Major Amendment. If you have any questions, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and Regulatory Counsel

MINOR AMENDMENT

NOV 13 2000

ANDA 40-385

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)

TO: APPLICANT: Barr Laboratories, Inc.

TEL: (914) 362-1100

ATTN: Christine Mundkur

FAX: ~~(914)~~ (845) 353-3859

FROM: Michelle Dillahunt

PROJECT MANAGER: 301-827-5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated July 23, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Methotrexate Tablets USP, 5 mg, 7.5 mg, 10 mg 15 mg.

Reference is also made to your amendment dated April 14, 2000.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (5 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 and labeling Comments Included.

11/9/00

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information from

11/13/2000 FDA FAX

8. [redacted]

9.

10.

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

1. Your response must also address the labeling deficiencies.

2. A satisfactory establishment evaluation is necessary for approval. We have requested an evaluation from the Office of Compliance.

Sincerely yours,

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

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

January 12, 2001

N/AM

ORIG AMENDMENT

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

REFERENCE: **ANDA 40-385**
METHOTREXATE TABLETS, USP 5 MG, 7.5 MG, 10 MG & 15 MG
MINOR AMENDMENT

Reference is made to our Abbreviated New Drug Application 40-385 dated July 23, 1999 and submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Methotrexate Tablets, USP 5 mg, 7.5 mg, 10 mg and 15 mg. Reference is also made to your facsimile dated March 9, 2000, Barr's major amendment dated April 14, 2000 and your facsimile dated November 13, 2000. The deficiencies identified in the November 13, 2000 facsimile and our responses are as follows:

A. DEFICIENCIES

COMMENT 1:

DMF _____ has been found deficient. The DMF holder has been notified by separate letter. Please respond to this deficiency only after you have learned that the DMF holder has responded.

RESPONSE:

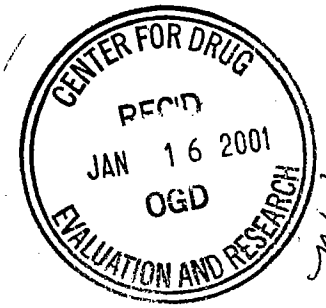
_____ the holder of DMF ____ has responded to the deficiencies on January 12, 2001.

COMMENT 2:

DMF _____ ., has been found deficient. The DMF holder has been notified by separate letter. Please respond to this deficiency only after you have learned that the DMF holder has responded.

RESPONSE:

_____, the holder of DMF ____ has responded to the deficiencies on November 13, 2000.



MW 1-22-01

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information from

1/12/2001 BARR LETTER

LABELING DEFICIENCIES:

COMMENT 1:

GENERAL COMMENTS – Your proposed proprietary names are under review. We defer comment at this time.

COMMENT 2:

CONTAINER (30's, 60's and 100's)

i. Storage Temperature Recommendation – include "Protect from light.".

ii. Warnings – Delete '[redacted].

COMMENT 3:

PHYSICIAN'S SAMPLE BOTTLE (4's) – See comments under CONTAINER.

COMMENT 4:

PHYSICIAN'S SAMPLE UNIT DOSE BLISTER (1's) – See GENERAL COMMENTS.

COMMENT 5:

PHYSICIANS'S SAMPLE UNIT DOSE BLISTER CARTON (1's) – See GENERAL COMMENTS.

COMMENT 6:

PHYSICIAN'S SAMPLE DISPENSER (10 unit dose cartons per dispenser) – See comments under GENERAL COMMENTS.

COMMENT 7:

INSERT

a. See GENERAL COMMENTS.

b. INDICATIONS AND USAGE

i. Neoplastic Diseases – Delete '[redacted]

c. PRECAUTIONS (Information for Patients) – Second paragraph – Delete the penultimate sentence which reads, "[redacted] Your product is not [redacted]

d. PRECAUTIONS (Organ System Toxicity; Neurologic) – Include the following to appear as the second and third sentences of paragraph one of this subsection:

Serious neurotoxicity, frequently manifested as generalized or focal seizures, has been reported with unexpectedly increased frequency among pediatric patients with acute lymphoblastic leukemia who were treated with intermediate – dose intravenous methotrexate (1 gm/m^2). Symptomatic patients were commonly noted to have leukoencephalopathy and/or microangiopathic calcifications on diagnostic imaging studies.

COMMENT 7 (continued)

NOTE: Although you are not seeking approval for the indication referenced above, we feel that it is important information for safe use of the drug. Although seizures are only documented in this situation, it may be reasonable that this could occur in other situations.

e. **ADVERSE REACTIONS (Adverse reactions in Psoriasis) – Include the following to appear as the last sentence in this subsection:**

Rarely, painful plaque erosions may appear (Pearce, HP and Wilson, BB: *Am Acad Dermatol* 35" 835-838, 1996).

f. **DOSAGE AND ADMINISTRATION (Psoriasis and Rheumatoid Arthritis) Revise the second paragraph of this subsection to read as follows:**

Weekly therapy may be instituted to provide doses over a range of 5 mg to 15 mg administered as a single weekly dose. All schedules should be continually tailored to the individual patient. An initial test dose may be given prior to the regular dosing schedule to detect any extreme sensitivity to adverse effects (see ADVERSE REACTIONS). Maximal myelosuppression usually occurs in seven to ten days.

Please revise your labels and labeling, as instructed above, and submit 4 copies of draft labels and labeling. We will not request final print labels and labeling until a determination has been made regarding the acceptability of your proposed proprietary name.

RESPONSE:

Barr has revised the labels and labeling as requested by the Agency. Please note that Barr received a telephone call on August 8, 2000 from Ms Theresa Watkins of Labeling Review Branch regarding the review of our proposed proprietary names. Ms Watkins informed that Trexall™ was found to be acceptable by the review committee. Upon receipt of this comment letter, Barr contacted Ms Watkins on November 16, 2000 to confirm the status of the proposed proprietary name. Ms Watkins confirmed that the proprietary name Trexall™ has been approved by the Agency and Barr could submit final printed labeling. Based on our discussion with Ms Theresa Watkins, we are providing final printed labeling in this amendment in Attachment 7. Side by side comparisons of the final printed labeling for Trexall™ with the previously submitted draft labeling for Trexall™ are also provided.

This amendment will be provided in electronic format within 30 days from the date of this letter. Barr Laboratories, Inc. will at that time, provide a declaration that the information in the electronic submission is the same as the information provided in the paper submission.

A Field Copy of this amendment has been forwarded to the Baltimore District Office. A Field Copy Certification is also provided.

This completes the present Minor Amendment. If you have any questions, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and Regulatory Counsel

Barr Laboratories, Inc.

Document Certification

Barr Laboratories, Inc. hereby certifies that field copy of this Minor Amendment for Methotrexate Tablets, USP 5 mg, 7.5 mg, 10 mg and 15 mg is being submitted to the Baltimore District office of the FDA. Barr Laboratories, Inc. further certifies that the field copy is a true copy of the material submitted to the Agency.

Christine Mundkur
Vice President, Quality and Regulatory Counsel
Barr Laboratories, Inc.

Jan. 12, 2001
Date

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

February 2, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

NEW CORRESP
NC

REFERENCE: **ANDA 40-385**
METHOTREXATE TABLETS, USP 5 MG, 7.5 MG, 10 MG & 15 MG
GENERAL CORRESPONDENCE

Reference is made to our Abbreviated New Drug Application 40-385 dated July 23, 1999 and submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Methotrexate Tablets, USP 5 mg, 7.5 mg, 10 mg and 15 mg. Reference is also made to your facsimile dated November 13, 2000 and Barr's minor amendment dated January 12, 2001.

As per a discussion between Ms. Angela Payne of the Labeling Review Branch, OGD, and Sharif Ahmed of Barr Laboratories, Inc. on February 2, 2001, we are submitting this correspondence to provide a revised package brochure.

Please note that in the labeling deficiency comment 7 d. of the November 13, 2000 facsimile, FDA requested the following:

> d. **PRECAUTIONS (Organ System Toxicity; Neurologic) – Include the following to appear as the second and third sentences of paragraph one of this subsection:**
>
> **Serious neurotoxicity, frequently manifested as generalized or focal seizures, has been reported with unexpectedly increased frequency among pediatric patients with acute lymphoblastic leukemia who were treated with intermediate – dose intravenous methotrexate (1 gm/m^2). Symptomatic patients were commonly noted to have leukoencephalopathy and/or microangiopathic calcifications on diagnostic imaging studies.**

Barr mistakenly "replaced" the second and third sentences of the paragraph with the above sentences instead of "adding" them and submitted the labeling in the January 12, 2001 minor amendment. Barr is now submitting corrected labeling that includes the two sentences that were mistakenly replaced. A side by side comparison of the affected sections of the previous labeling and the proposed labeling is provided along with 12 copies of final print labeling.

We apologize for the mistake. If you have any questions, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

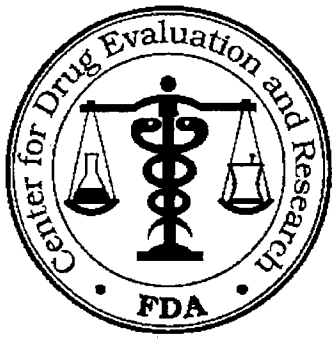
Christine Mundkur
Vice President, Quality and Regulatory Counsel

MINOR AMENDMENT

ANDA 40-385

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)

FEB 6 2001



TO: APPLICANT: Barr Laboratories, Inc. TEL: (845) 362-1100

ATTN: Christine Mundkur FAX: (845) 353-3859

FROM: Michelle Dillahunt PROJECT MANAGER: 301-827-5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated July 23, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Methotrexate Tablets USP, 5 mg, 7.5 mg, 10 mg, and 15 mg.

Reference is also made to your amendment(s) dated: January 12, 2001.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (1 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:

2/6/01 MD

FEB 16 2001

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-385 APPLICANT: Barr Laboratories, Inc.

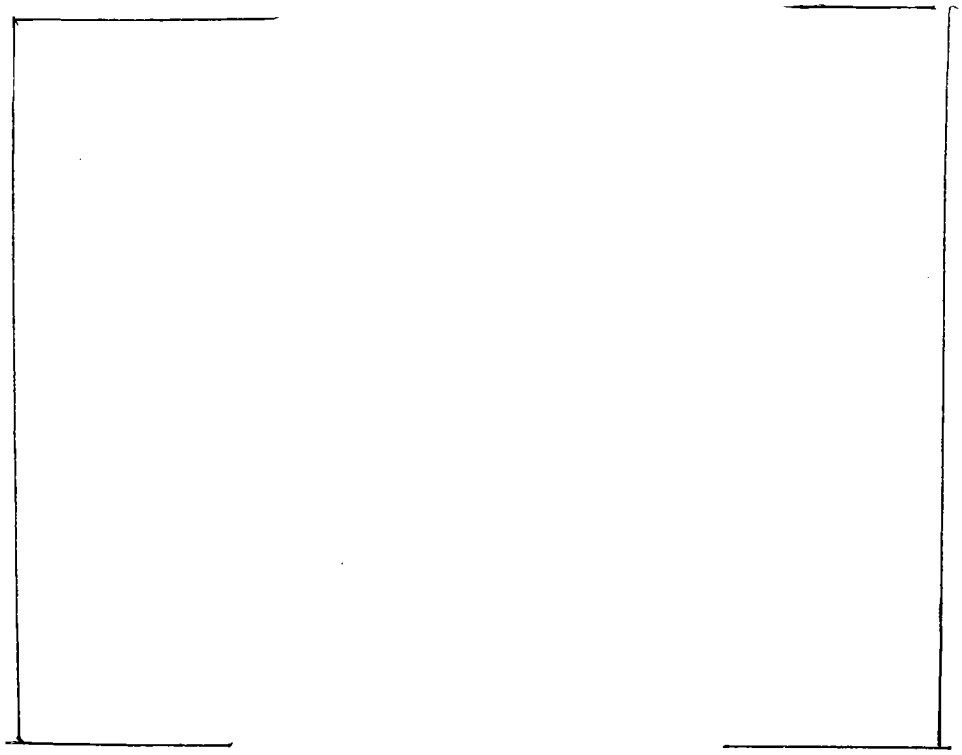
DRUG PRODUCT: Methotrexate Tablets USP, 5mg, 7.5mg, 10mg, 15mg.

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1.

2.



Sincerely yours,

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

barr Laboratories, Inc.

2 Quaker Road
P.O. Box 2900
Pomona, NY 10970
914-362-1100

Fax Transmission

Date: February 8, 2001

To: Michelle Dillahunt
Project Manager
Phone Number: (301) 827-5848
Fax Number: (301) 594-0180

From: Sharif Ahmed
Manager of Regulatory Affairs
Phone Number: (913) 353-8476
Fax Number: (914) 353-3859

Number of Pages (including cover): 9

Message:

Please refer to our pending application ANDA 40-385 for Methotrexate Tablets, USP 5 mg, 7.5 mg, 10 mg and 15 mg and the deficiency letter of February 6, 2001. We would like to discuss comment 2 with the chemistry reviewer or the team leader. We want to make sure we understand the reason for Agency's concern expressed in this comment before we respond to this deficiency.

I will appreciate if you would set up a conference call. Please call us at (845) 353-8432 some time tomorrow morning or at your convenience. Christine Mundkur, Vice President of Quality and Regulatory Counsel and Sharif Ahmed, Manager of Regulatory Affairs will participate in the discussion. Please confirm when you will be calling so we will make ourselves available.

Sincerely,
Sharif Ahmed

Verification Name/Number: _____

MD
Pls advise them it is policy to require full term data if accelerated show adverse trends. If they still want TCon, set up for you + I for [illegible] since I do not know my

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

February 15, 2001

NDA ORIG AMENDMENT
N/Am

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

REFERENCE: **ANDA 40-385**
METHOTREXATE TABLETS, USP 5 MG, 7.5 MG, 10 MG & 15 MG
MINOR AMENDMENT

Reference is made to our Abbreviated New Drug Application 40-385 dated July 23, 1999 and submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Methotrexate Tablets, USP 5 mg, 7.5 mg, 10 mg and 15 mg. Reference is also made to your facsimile dated March 9, 2000, Barr's major amendment dated April 14, 2000, your facsimile dated November 13, 2000, Barr's minor amendment dated January 12, 2001 and your facsimile dated February 6, 2001. The deficiencies identified in the February 6, 2001 facsimile and our responses are as follows:

A. DEFICIENCIES

COMMENT 1:

[redacted]

RESPONSE:

Following the Agency comment we reviewed our response to comment 7 and found that the statements made in the response was not accurate. We apologize for the inadvertent mistake and any confusion this may have caused. Following is a clarification regarding the validation study and response to the Agency comment 7.

[redacted]

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2/15/2001 BARR LETTER

Barr Laboratories, Inc.

Document Certification

Barr Laboratories, Inc. hereby certifies that a field copy of this Minor Amendment for Methotrexate Tablets, USP 5 mg, 7.5 mg, 10 mg and 15 mg is being submitted to the Baltimore District office of the FDA. Barr Laboratories, Inc. further certifies that the field copy is a true copy of the material submitted to the Agency.

Christine Mundkur
Vice President, Quality and Regulatory Counsel
Barr Laboratories, Inc.

2/15/01
Date

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

February 22, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

NDA DRUG AMENDMENT

REFERENCE: **ANDA 40-385**
METHOTREXATE TABLETS, USP 5 MG, 7.5 MG, 10 MG & 15 MG
AMENDMENT TO FEBRUARY 15 MINOR AMENDMENT

Reference is made to our Abbreviated New Drug Application 40-385 dated July 23, 1999 and submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Methotrexate Tablets, USP 5 mg, 7.5 mg, 10 mg and 15 mg. Reference is also made to your facsimile dated March 9, 2000, Barr's major amendment dated April 14, 2000, your facsimile dated November 13, 2000, Barr's minor amendment dated January 12, 2001, your facsimile dated February 6, 2001 and Barr's minor amendment dated February 15, 2001.

Reference is also made to a conference call with Michael Smela, Jr. and Michelle Dillahunt of the Office of Generic Drugs and Christine Mundkur and Sharif Ahmed of Barr Laboratories, Inc. concerning the February 6, 2001 deficiency letter and Barr's response to that. Following the discussion, Barr decided to amend the February 15, 2001 minor amendment.

The deficiencies identified in the February 6, 2001 facsimile and Barr's amended responses are as follows:

A. DEFICIENCIES

COMMENT 1:

[redacted]

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
FEB 23 2001
OGD

RESPONSE:

Following the Agency comment we reviewed our response to comment 7 and found that the statements made in the response was not accurate. We apologize for the inadvertent mistake and any confusion this may have caused. Following is a clarification regarding the validation study and response to the Agency comment 7.

[redacted]

Redacted 1 page(s)

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confidential commercial

information from

2/22/2001 BARR LETTER

At this time, Barr also requests to withdraw the additional drug substance source of ———— without prejudice to filing at a future date.

The updated stability data for the 5 mg and 15 mg through 36 months, 7.5 mg and 10 mg through 18 months are provided in Attachment 1.

A field copy of this amendment has been forwarded to the Baltimore District Office. A Field Copy Certification is also provided.

This completes the present amendment. If you have any questions, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and Regulatory Counsel