

**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**

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<sup>®</sup> 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<sup>®</sup> 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/

*ES 3/9/01*  
*SC 3/12/01* *for M Smak*

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F/T by: DJ 3/8/01

APPROVAL

*3/12/01*  
*3/13/01*  
*3/21/01*  
*3/26/01*

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**ANDA 40-385**

**APPROVED LABELING**

Rx only

MAR 21 2001

APPROVED



21009270101



Trexall™

(methotrexate tablets, USP)



Revised JANUARY 2001  
21009270101

**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.

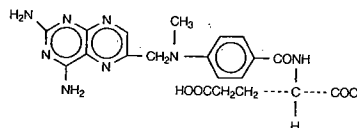
PATIENTS SHOULD BE CLOSELY MONITORED FOR BONE MARROW, LIVER, LUNG AND KIDNEY TOXICITIES. (See **PRECAUTIONS**.)

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<sup>2</sup> or less, methotrexate is generally well absorbed with a mean bioavailability of about 60%. The absorption of doses greater than 80 mg/m<sup>2</sup> 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<sub>MAX</sub>: 0.11 to 2.3 micromolar after a 20 mg/m<sup>2</sup> dose) has been reported. Significant interindividual variability has also been noted in time to peak concentration (T<sub>MAX</sub>: 0.67 to 4 hours after a 15 mg/m<sup>2</sup> 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 uninfamed 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 polyglutamate 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<sup>2</sup>). 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 reinstated, 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 intrathecal 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<sup>3</sup>) was seen in 2 patients, thrombocytopenia (platelets <100,000/mm<sup>3</sup>) 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 pre-existing liver damage or impaired hepatic function.

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 (Roienigk 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 (Roienigk grade IIIb or IV).<sup>2</sup>

**Infection or Immunologic States:** Methotrexate should be used with extreme caution in the presence of acute 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<sup>2</sup>). 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 alkalization 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<sup>3</sup>),

**Incidence 1% to 3%:** Rash/pruritus/dermatitis, diarrhea, alopecia, leukopenia (WBC less than 3000/mm<sup>3</sup>), 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 (Roienigk, 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 overdoses 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 overdose, hydration and urinary alkalization may be necessary to prevent the precipitation of methotrexate and/or its metabolites in the renal tubules. Generally speaking, neither hemodialysis nor peritoneal dialysis has 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).

#### DOSEAGE 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 interspersed between courses, until any manifesting toxic symptoms subside. The effectiveness of therapy is ordinarily evaluated by 24-hour quantitative analysis of urinary chorionic gonadotropin (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.

Choriocarcinoma 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<sup>2</sup> in combination with 60 mg/m<sup>2</sup> 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<sup>2</sup>. 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 interspersed 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 reinstating 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 Dose 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.<sup>1-8</sup> There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

**HOW SUPPLIED:**

**Trexal™** (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 **928/7.5** 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.
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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.

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

Marketed by:  
**DuPont Pharma**  
Wilmington, DE 19880

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



40-385

Approved

3/21/01

Each tablet contains methotrexate sodium equivalent to 5 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  
2129927010101

**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:** See package brochure.  
 Manufactured by: BARR LABORATORIES, INC., Pomona, NY 10970

**Marketed by:** DuPont Pharma Wilmington, DE 19880

NDC 0555-0927-01



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R9-00  
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**Trexall™**  
 (methotrexate tablets, USP)

**5 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 0555-0927-02



Exp: Lot: SAMPLE

Each tablet contains methotrexate sodium equivalent to 5 mg of Methotrexate.  
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**Trexall™**  
 (methotrexate tablets, USP)

**5 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.  
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Exp: Lot: SAMPLE

Each tablet contains methotrexate sodium equivalent to 5 mg of Methotrexate.  
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**Trexall™**  
 (methotrexate tablets, USP)

**5 mg**



**Rx only**  
**4 Tablets**

PROFESSIONAL SAMPLE

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**Usual Dosage:** See package brochure.  
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Exp: Lot: SAMPLE

40-385

Each tablet contains methotrexate sodium equivalent to 7.5 mg of Methotrexate.  
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 Protect from light.

R9-00  
2120282020101

**Trexall™**  
(methotrexate  
tablets, USP)

7.5 mg

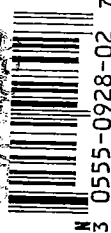


Rx only  
100 Tablets

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3 0555-0928-02 7

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R9-00  
2120282020101

**Trexall™**  
(methotrexate  
tablets, USP)

7.5 mg

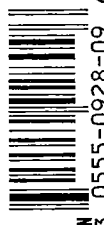


Rx only  
60 Tablets

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NDC 0555-0928-09



3 0555-0928-09 6

Exp: Lot:  
SAMPLE

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**Trexall™**  
(methotrexate  
tablets, USP)

7.5 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:** See package brochure.  
**Manufactured by:** BARR LABORATORIES, INC., Pomona, NY 10970

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DuPont Pharma  
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NDC 0555-0928-01



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Exp: Lot:  
SAMPLE

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**Trexall™**  
(methotrexate  
tablets, USP)

7.5 mg



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.  
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3 0555-0928-55 3

Exp: Lot:  
SAMPLE

PROFESSIONAL SAMPLE

40-385

Each tablet contains methotrexate sodium equivalent to 10 mg of Methotrexate.  
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**Trexall<sup>®</sup>**  
**(methotrexate tablets, USP)**



PROFESSIONAL SAMPLE

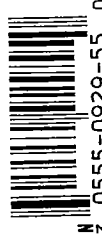
Rx only  
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Pomona, NY 10970

NDC 0555-0929-55



Exp: SAMPLE  
Lot:



Each tablet contains methotrexate sodium equivalent to 10 mg of Methotrexate.  
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PROFESSIONAL SAMPLE

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DuPont Pharma  
Wilmington, DE 19880



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

NDC 0555-0929-01



Exp: SAMPLE  
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  
2120929050101

**Trexall<sup>®</sup>**  
**(methotrexate tablets, USP)**



PROFESSIONAL SAMPLE

Rx only  
60 Tablets

Marketed by:  
DuPont Pharma  
Wilmington, DE 19880



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

NDC 0555-0929-09



Exp: SAMPLE  
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<sup>®</sup>**  
**(methotrexate tablets, USP)**



PROFESSIONAL SAMPLE

Rx only  
100 Tablets

Marketed by:  
DuPont Pharma  
Wilmington, DE 19880



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

NDC 0555-0929-02



Exp: SAMPLE  
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)



**Rx only**  
100 Tablets

Marketed by:  
**DuPont Pharma**  
Wilmington, DE 19880

**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

NDC 0555-0945-02



**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)



**Rx only**  
60 Tablets

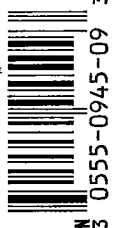
Marketed by:  
**DuPont Pharma**  
Wilmington, DE 19880

**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

NDC 0555-0945-09



**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)



**Rx only**  
30 Tablets

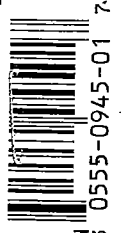
Marketed by:  
**DuPont Pharma**  
Wilmington, DE 19880

**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

NDC 0555-0945-01



**SAMPLE**

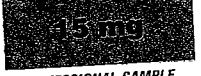
Exp:  
Lot:

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)



**Rx only**  
4 Tablets

Marketed by:  
**DuPont Pharma**  
Wilmington, DE 19880

**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

NDC 0555-0945-55



**SAMPLE**

Exp:  
Lot:

