CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 40-233

Approval Letter

ANDA 40-233

JUN 17 1999

Duramed Pharmaceuticals, Inc.
Attention: John R. Rapoza
5040 Lester Road
Cincinnati, OH 45213

Dear Sir:

This is in reference to your abbreviated new drug application dated December 20, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Methotrexate Tablets USP, 2.5 mg.

Reference is also made to your amendments dated October 13, and May 20, 1999.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Methotrexate Tablets USP, 2.5 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Methotrexate Tablets, 2.5 mg, of Lederle Laboratories). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, 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. 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,

/S/

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

6/17/99

cc: ANDA 40-233

/S/

Endorsements:

6/7/99

6/7/99

/S/

8/99

6/11/99

Enclosed, Pending acceptable ESR

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 40-233

FINAL PRINTED LABELING

METHOTREXATE Tablets, USP

R 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.

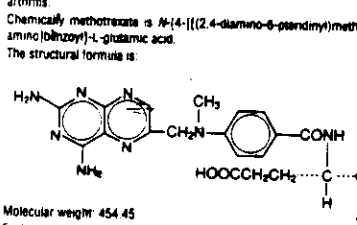
1. Methotrexate has been reported to cause fetal death and/or congenital anomalies. Therefore, it is not recommended for women of childbearing potential unless there is clear medical evidence that the benefits can be expected to outweigh the considered risks. Pregnant women with psoriasis or rheumatoid 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. Reaction 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.

DESCRIPTION

Methotrexate (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]methylamino]benzoyl]-L-glutamic acid.

The structural formula is:



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

Each tablet for oral administration contains methotrexate sodium equivalent to 2.5 mg of methotrexate. In addition, each tablet contains the following inactive ingredients: lactose monohydrate, magnesium stearate and pregelatinized starch.

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 [illegible] areas. 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/m² or less, methotrexate is generally well absorbed with a mean bioavailability of about 60%. The absorption of doses greater than 80 mg/m² 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/m² dose) has been reported. Significant interindividual variability has also been noted in time to peak concentration (T_{max} 0.67 to 4 hrs after a 15 mg/m² 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. Accumulation of this metabolite may become significant at the high doses used in osteogenic sarcoma. 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/m²). For patients receiving high doses of methotrexate, the terminal half-life is 8 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

Methotrexate is indicated in the treatment of gestational choriocarcinoma, chorioadenoma destruens and hydatidiform mole.

In acute lymphocytic leukemia, methotrexate is indicated in maintenance therapy in combination with other chemotherapeutic agents. Methotrexate is also indicated in the treatment of meningeal leukemia.

Methotrexate is used alone or in combination with other anti-cancer 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

Methotrexate is 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

Methotrexate is 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 breastfed 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. (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 (eg, 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 histologic changes 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 and 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.

Patients receiving concomitant therapy with methotrexate and etretinate or other retinoids should be monitored closely 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, 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

METHOTREXATE TABLETS, USP

3248

METHOTREXATE TABLETS, USP

[illegible] treatment with low-dose oral methotrexate which have regressed somewhere 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/mm³) was seen in 2 patients, thrombocytopenia (platelets <100,000/mm³) 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.

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%) case of cirrhosis. Of the 64 cases of fibrosis, 50 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 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).[4]

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.

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 (eg, pleural [illegible] 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 PRECAUTIONS 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 sensations, leukoencephalopathy, or encephalopathy.

Infection: There have been rare 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, and reversible lymphomas. Anaphylactoid reactions have been reported.

Adverse Reactions in Double-Blind Rheumatoid Arthritis Studies

The approximate incidences of methotrexate attributed (ie, 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/mm³).

Incidence 1% to 3%: Rash/pruritus/dermatitis, diarrhea, alopecia, leukopenia (WBC less than 3000/mm³), 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.

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. Neither hemodialysis nor peritoneal dialysis have been shown to improve methotrexate elimination.

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. Methotrexate sodium injection and for injection may be given by the intramuscular, intravenous, intra-arterial or intrathecal route. However, the preserved formulation contains Benzyl Alcohol and must not be used for intrathecal or high dose therapy.

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 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.

Choriodenoma 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 and young adolescents is the most responsive to present day chemotherapy. In young adults and older patients, clinical remission is more difficult to obtain and [illegible] Methotrexate alone or in combination with steroids was used initially for induction of remission of acute lymphoblastic leukemias. More recently combosteroid 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/m² in combination with 60 mg/m² 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/m². 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 anti-tumor 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.)

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 dose 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.[5-8] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

Methotrexate tablets, USP, 2.5 mg, are yellow, oval and debossed on the scored side with "[illegible]" and "509" in bottles of 36 (NDC 51285-509-36) and 100 (NDC 51285-509-02).

Store at 25°C (77°F), excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

Protect From Light.

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Mfd. for: DURAMED PHARMACEUTICALS, INC.
Cincinnati, OH 45213 USA
by: KIEL LABORATORIES, INC.
Gainesville, GA 30504 USA

I063248 REV. 04/99

REFERENCES

1. Roenigk HH, Auerbach R, Maibach HI, et al. Methotrexate in Psoriasis: Revised Guidelines. *J Am Acad Dermatol* 1988; 19:145-156.
2. Kremer JM, et al. Methotrexate for Rheumatoid Arthritis: Suggested Guidelines for Monitoring Liver Toxicity. *Arth Rheum* 1994; 37:316-328.
3. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402.
4. AMA Council Report. Guidelines for Handling Parenteral Antineoplastics. *JAMA*, March 15, 1985.
5. National Study Commission on Cytotoxic Exposure—Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, ScD., Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.
6. Clinical Oncological Society of Australia: Guidelines And Recommendations For Safe Handling Of Antineoplastic Agents. *Med J Australia* 1983; 1:426-428.
7. Jones RB, et al. Safe handling of chemotherapeutic agents: A report from the Mount Sinai Medical Center, Ca. - *A Cancer Journal for Clinicians*, 1983; (Sept/Oct) 258-263.
8. American Society of Hospital Pharmacists. Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. *Am J Hosp Pharm* 1990; 47:1033-1049.

Exp Date

Lot No.

DURA med

NDC 51285-509-02

Methotrexate

Tablets, USP

2.5mg ℞ only

This package not for household dispensing.

100 Tablets

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

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

Mfd for: DURAMED PHARMACEUTICALS, INC. CINCINNATI, OH 45213 USA

by: BEL LABORATORIES, INC. GAINESVILLE, GA 30504

LM0404 REV. 04/05

0 28176 50902 8

Exp Date

Lot No.

DURA med

NDC 51285-509-02

Methotrexate

Tablets, USP

2.5mg ℞ only

This package not for household dispensing.

100 Tablets

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

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

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by: BEL LABORATORIES, INC. GAINESVILLE, GA 30504

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by: BEL LABORATORIES, INC. GAINESVILLE, GA 30504

LM0404 REV. 04/05

0 28176 50902 8

DUBAmed

NDC 51285-509-36

Methotrexate

Tablets, USP

2.5mg ℞ only

This package not for household dispensing

36 Tablets

Lot No:

Exp. Date:

0 28176 50936 3

DUBAmed

NDC 51285-509-36

Methotrexate

Tablets, USP

2.5mg ℞ only

This package not for household dispensing

36 Tablets

Lot No:

Exp. Date:

0 28176 50936 3

DUBAmed

NDC 51285-509-36

Methotrexate

Tablets, USP

2.5mg ℞ only

This package not for household dispensing

36 Tablets

Lot No:

Exp. Date:

0 28176 50936 3

DUBAmed

NDC 51285-509-36

Methotrexate

Tablets, USP

2.5mg ℞ only

This package not for household dispensing

36 Tablets

Lot No:

Exp. Date:

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Exp Date

Lot No:

DURA med

NDC 51285-509-02

Methotrexate

Tablets, USP

2.5mg ℞ only

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

Mfd for: DURAMED PHARMACEUTICALS, INC. CINCINNATI, OH 45213 USA

by: IDEL LABORATORIES, INC. GAINESVILLE, GA 30504

L050504 REV. 04/05

0 28176 50902 8

Exp Date

Lot No:

DURA med

NDC 51285-509-02

Methotrexate

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2.5mg ℞ only

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by: IDEL LABORATORIES, INC. GAINESVILLE, GA 30504

L050504 REV. 04/05

0 28176 50902 8

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 40-233

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 40-233

3. NAME AND ADDRESS OF APPLICANT
Duramed Pharmaceuticals, Inc.
5040 Lester Road
Cincinnati, OH 45213

4. LEGAL BASIS FOR SUBMISSION
Expired patent.
Listed Drug Product: Methotrexate Sodium Tablets (Lederle Laboratories)

The indications the proposed drug product is going to be used for, active ingredient, route of administration, dosage form, strength and labeling is same as listed drug product.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None used.

7. NONPROPRIETARY NAME
Methotrexate Tablets USP, 2.5 mg

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

9. AMENDMENTS AND OTHER DATES:
FIRM:
Original submission: 12-20-96
Amendment: 3-13-97
Amendment: 4-16-97
Major Amendment: 10-9-98 (Response to 7-18-98 NA letter)
* Fax Amendment: 5-20-99 (Response to 4-17-99 letter)

FDA:
Refuse to file Letter: 2-28-97
Date acceptable for filing: 3-14-97
[Acknowledgement Letter issued on: 4-7-97]
NA letter: 7-18-98
NA letter: 4-27-99

10. PHARMACOLOGICAL CATEGORY
Antineoplastic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
ANDA 81-099..Barr... Approved on 10-15-90
ANDA 81-235..Mylan.. Approved on 5-15-92
ANDA 40-054..Roxane..Approved on 8-1-94

13. DOSAGE FORM
Tablets

14. POTENCY
2.5 mg

15. CHEMICAL NAME AND STRUCTURE
SEE CR # 1.

16. RECORDS AND REPORTS
N/A

17. COMMENTS
1. DMF for manufacturer active substance is adequate per M. Shaikh's review dated 6-24-97. No new information is submitted.
2. Labeling is acceptable as of 5-24-99.
3. Bio Review is acceptable.
4. EER status for all the facilities is withhold.
5. Approved ANDA 40-054 is consulted to conduct review of this ANDA with respect to release and stability specifications.

18. CONCLUSIONS AND RECOMMENDATIONS
Approved pending acceptable EER status.

19. REVIEWER:
Mujahid L. Shaikh

DATE COMPLETED:
5-27-99

Endorsements:

Page(s) 10

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

Chemist Review # 3

APR 27 1999

38. Chemistry Comments to be Provided to the Applicant

ANDA: 40-233 APPLICANT: Duramed Pharmaceuticals, Inc.

DRUG PRODUCT: Methotrexate Tablets USP, 2.5 mg

The deficiencies presented below represent Facsimile deficiencies.

A. Deficiencies:

ıire.

2. Your proposed blend uniformity specification as a routine in-process control is acceptable but you failed to include relative standard deviation (RSD) of Please be advised that test sample should be size of 1-3 tablets.

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

1. A satisfactory cGMP compliance of all facilities listed in your application is required prior to the approval of this application.

2. Your bioequivalence data is pending review.

6. You must also address the labeling deficiencies in your response.

Sincerely yours,

/S/

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

TABLE OF CONTENTS

Duramed Pharmaceuticals, Inc.

ANDA # 40-233 Methotrexate Tablets, USP, 2.5 mg

October 9, 1998 Amendment

JUL 19 1997

38. Chemistry Comments to be Provided to the Applicant

ANDA: 40-233 APPLICANT: Duramed Pharmaceuticals, Inc.

DRUG PRODUCT: Methotrexate Tablets USP, 2.5 mg

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

Page(s) 1

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

Christy Nora

#78

7/18/97

4.

5. Your bioequivalence data is pending review.

6. You must also address the labeling deficiencies in your response.

Sincerely yours,

/S/

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

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 40-233

BIOEQUIVALENCE REVIEW(S)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA/AADA: 40-233 APPLICANT: Duramed

DRUG PRODUCT: Methotrexate, USP, 2.5 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 U.S.P. 23.

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,

/S/

Rabindra N. Patnaik, Ph.D.
Acting Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

Methotrexate Tablets	Duramed
2.5 mg Tablets	Cincinnati, OH
ANDA #40-233	Submission Date: 12/20/96
Reviewer: Moo Park	

REF PRODUCT	Methotrexate Sodium Tablets, 2.5 mg, manufactured by Lederle Laboratories
BE STUDY DESIGN	Open-label, balanced, randomized, two period, single dose, crossover study
STUDY SITE	A
STUDY SUMMARY	1. **Pharmacokinetic and statistical evaluation:** Twenty-six healthy male subjects enrolled and all 26 completed the crossover study. Peak mean plasma levels for the test and reference products were 128.9 ng/mL at 0.67 hour and 131.6 ng/mL at 0.83 hour, respectively. The LSMEANS are comparable for the test and reference products. The Test/Reference ratios range 0.97-1.02. The 90% confidence intervals for the log-transformed AUCT, AUCI and CMAX are within the acceptable range of 80-125%. 2. **Drug products:** The assay and content uniformity data for the test and reference products are acceptable. The batch size of the test product was tablets. 3. **Medical events:** No serious medical events were reported during the study.
BIOASSAY VALIDATION	Pre-study and within-study validation data are acceptable.
DISSOLUTION	The test product, lot #GA194, met the USP dissolution specifications.
WAIVER	n/a

/S/

INITIAL: _____ DATE: 9/8/97
REVIEWER: Moo Park, Ph.D.
BRANCH: III

/S/
INITIAL: _____ DATE: 9/9/97
TEAM LEADER: Ramakant M. Mhatre, Ph.D.
BRANCH: III

/S/
INITIAL: _____ DATE: 1/16/98
DIRECTOR: ~~Nicholas Fleischer, Ph.D.~~
DIVISION OF BIOEQUIVALENCE

INITIAL: _____ DATE: _____
DIRECTOR
OFFICE OF GENERIC DRUGS

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

Methotrexate Tablets	Duramed
2.5 mg Tablets	Cincinnati, OH
ANDA #40-233	Submission Date: 12/20/96
Reviewer: Moo Park	

REF PRODUCT	Methotrexate Sodium Tablets, 2.5 mg, manufactured by Lederle Laboratories
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BIOASSAY VALIDATION	Pre-study and within-study validation data are acceptable.
DISSOLUTION	The test product, lot #GA194, met the USP dissolution specifications.
WAIVER	n/a

INITIAL: _____ DATE: 7/8/97
REVIEWER: Moo Park, Ph.D.
BRANCH: III

INITIAL: _____ DATE: 7/9/97
TEAM LEADER: RamaKant M. Mhatre, Ph.D.
BRANCH: III

INITIAL: _____ DATE: 1/16/98
DIRECTOR: ~~Nicholas Fleischer, Ph.D.~~
DIVISION OF BIOEQUIVALENCE

INITIAL: _____ DATE: _____
DIRECTOR
OFFICE OF GENERIC DRUGS

[redacted]

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA/AADA: 40-233 APPLICANT:Duramed

DRUG PRODUCT: Methotrexate, USP, 2.5 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 U.S.P. 23.

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,

/S/

Rabindra N. Patnaik, Ph.D.
Acting Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

NOV 13 1997

Methotrexate Tablets
2.5 mg Tablets
ANDA #40-233
Reviewer: Moo Park
Filename: 40233sd.d96

Duramed
- Cincinnati, OH
Submission Date: 12/20/96

Review of an *in vivo* Bioequivalence Study and Dissolution Data

I. Objective

The objective of this study was to determine the bioequivalence of Methotrexate Tablets, USP, 2.5 mg, manufactured by Duramed Pharmaceuticals, Inc., relative to the listed drug product, Methotrexate Sodium Tablets, 2.5 mg, manufactured by Lederle Laboratories, in healthy, normal males under fasting conditions.

II. Background

Methotrexate is N-[4-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-L-glutamic acid. Methotrexate is an antimetabolite used in the treatment of neoplastic tumors as well as some non-neoplastic diseases such as severe psoriasis, and adult rheumatoid arthritis. The enzyme dihydrofolate reductase (DHFR) is the site of action for this antifolate drug. 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 nucleosides and thymidate. In this way, DNA and RNA synthesis, repair and cellular replication is disrupted.
The mechanism of action in rheumatoid arthritis is unknown. Methotrexate is an antimetabolite used in the treatment of certain neoplastic diseases (leukemia, lymphomas, mycosis fungoides, osteosarcoma), severe psoriasis, and adult rheumatoid arthritis. The most frequently reported adverse reactions include mouth sores, nausea, abdominal distress, and a decrease in the number of white blood cells. Oral dosing of methotrexate appears to be dose dependent. Peak serum levels are reached within 1 to 2 hours. At doses of 30 mg/m^2 or less, methotrexate is generally well absorbed with a mean bioavailability of about 60%. Methotrexate is metabolized via several routes including

partial metabolism by the intestinal flora, in addition to hepatic and intracellular metabolism. A small amount of metabolism to 7-hydroxymethotrexate may occur at doses commonly prescribed, but this metabolite is less effective in the competitive inhibition of DHFR. The drug is approximately 50% bound to serum proteins, primarily albumin. Renal excretion, specifically glomerular filtration and active tubular secretion, is the primary route of elimination. Nonlinear elimination due to saturation of renal tubular resorption can occur. Methotrexate therapy is available in tablets or injection. Methotrexate for oral administration is available only in tablets containing a quantity of methotrexate sodium equivalent to 2.5 mg of the base. Methotrexate is administered orally, IM or IV over courses of weeks to months depending on the indication and disease state. Dosages range from 2.5 mg every 12 hours to 15 or 30 mg per day.

III. Study Details

Protocol No. KDI-508

Applicant Duramed

Study sites

Investigator:

Study dates Period 1: 8/24/96 - 8/25/96
Period 2: 8/31/96 - 9/01/96

Study design This was an open-label, balanced, randomized, two period, single dose, crossover study in healthy, normal males. The protocol specified dosing of 26 volunteers with 26 to complete.

Subjects

Twenty-six healthy male subjects were recruited and 26 completed the crossover study. The subjects were:

- Age 18-40
- Weight within 15% of ideal body weight
- No clinically significant abnormalities
- Normal clinical laboratory values

Drug products

Test product: Methotrexate Tablets, USP, 2.5 mg, GA 194, Expiration Date: 5/98, Duramed Pharmaceuticals, Inc. Batch Size: (theoretical); 407,300 (actual yield) tablets

Reference Product: Methotrexate Sodium Tablets, 2.5 mg, Lot 397-336, Expiration Date: 11/97, Lederle Laboratories.

Dosing

In this study, subjects are dosed with 2 x 2.5 mg tablets twice, once for each period.

Food and fluid

Prior to each period there was an overnight fast of at least 10 hours. Water was consumed ad libitum except within 1 hour before and after dosing. Water (240 mL at room temperature) was consumed at the time of dosing. Four (4) hours after dosing a standardized meal was served. No other food or beverage was allowed from 12 hours prior to dosing until 4 hours after dosing. Meal plans were identical for all periods.

Housing

Subjects were admitted to the research center the evening prior to dosing and were discharged after the 24-hour post-dose blood sample was obtained. Subjects were discharged at the end of Period 2 following receipt of a post-study physical examination.

Washout

There was a one week washout period between the start of each of the dosing periods.

Blood samples	During each period, plasma samples were obtained from blood drawn into heparinized tubes at 0 (pre-dose), 0.25, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16 and 24 hours after administration of the dose. The blood samples were centrifuged at -4°C , plasma collected, flash frozen within 5 minutes of harvesting and stored at -20°C until shipped for analysis. See the *eport* for exceptions to draw times, which were incorporated into the statistical analyses.
IRB	Duramed secured the permission of the in writing on 7/9/96.
Informed consent	Subject Consent Form was signed by each subject who participated in the study.
Assay method for blood samples	
Analytes	Methotrexate
PK analysis	AUCT, AUCI, CMAX, TMAX, KE, and THALF were calculated.
Statistical analysis	90% confidence intervals were calculated for log-transformed AUCT, AUCI and CMAX.

IV. Bioanalytical Method Validation

Plasma methotrexate was analyzed using detection over a concentration range of ng/mL.

A. Pre-study Validation

The pre-study validation report for plasma methotrexate assay was prepared and signed as of 7/26/96.

Table IV-1. Pre-Study Validation for Plasma Methotrexate

Assay method:	internal standard was
Specificity:	No significant interference from endogenous components or other sources.
Sensitivity:	The limit of quantitation was set at 5 ng/mL for methotrexate.
Linearity:	Weighted ($1/C^2$) least squares regression was used. Standard curve was prepared in the concentration range of 5-500 ng/mL. Correlation coefficient was 0.9985.
Precision and accuracy:	Between assay for methotrexate quality control samples (5-400 ng/mL): 89.4-100.4% accuracy with 4.4-12.1% CV. Within assay for methotrexate quality control samples (5-400 ng/mL): 92.2-97.5% accuracy with 2.8-12.8% CV.
Recovery:	methotrexate: Absolute mean recovery of 63.2-72.3% with %CV of 10.6-14.0 for 10-400 ng/mL range. Internal standard (aminopterin): Absolute mean recovery of 46.0-59.9% with 9.6-17.1% CV.
Stability:	Long term stability for methotrexate: 3.5 month at -20°C. Stability data acceptable. Short term stability for methotrexate: 4 hours at RT. Stability data acceptable. Freeze-thaw stability for methotrexate: 3 cycles. Stability data acceptable. Extract stability for methotrexate: 48 hours at RT. Stability data acceptable.

B. Within-study Validation

Precision and accuracy of the assay of the quality control samples and back calculated standard curve samples used in the fasting study are shown in Table IV-2. The within-study

validation data are acceptable.

Table IV-2. Within-Study Precision and Accuracy
Methotrexate

Precision and accuracy:	Quality control samples (10-400 ng/mL): 95.8-101% accuracy with 2.83-14.8% CV. Standard curve samples (5-500 ng/mL): 99.5-100.8% accuracy with 4.82-9.9% CV.

V. Pharmacokinetic and Statistical Evaluation of Study Data

Subjects: All twenty-six healthy male subjects who enrolled completed the crossover study. Data from all subjects were used in the pharmacokinetic/statistical evaluation.

Medical events: A total of two medical events (2 for the reference product involving Subject #23.) were reported. No serious medical events were reported during the study.

Evaluation of study data: Reviewer recalculated all the pharmacokinetic parameters and statistics and the results of the recalculation are in agreement with the sponsor's submission.

1. Mean plasma methotrexate levels

Mean plasma methotrexate levels for the test and reference products under fasting conditions were comparable to each other as shown in Table V-1 and Fig. P-1. Peak mean plasma levels for the test and reference products were 128.9 ng/mL at 0.67 hour and 131.6 ng/mL at 0.83 hour, respectively.

TABLE V-1. MEAN PLASMA Methotrexate LEVELS FOR TEST AND REFERENCE PRODUCTS
UNDER FASTING CONDITIONS
UNIT: PLASMA LEVEL=NG/ML TIME=HRS
MEAN1=TEST; MEAN2=REFERENCE; RMEAN12=MEAN1/MEAN2 RATIO
SD=STANDARD DEVIATION
Test Lot #GA194; Ref Lot #397-336

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.25	18.15	15.34	13.68	15.09	1.33
0.5	97.04	39.82	82.55	40.27	1.18
0.67	128.88	40.53	124.13	44.97	1.04
0.83	128.72	33.99	131.59	39.06	0.98
1	122.93	32.43	126.14	32.96	0.97
1.25	110.18	33.27	115.81	27.40	0.95
1.5	95.37	24.85	100.71	24.89	0.95
2	75.37	18.85	78.42	15.02	0.96
2.5	62.39	15.01	63.05	11.39	0.99
3	51.60	14.27	52.51	10.60	0.98
4	35.98	9.72	36.20	8.61	0.99
5	30.15	9.19	30.77	8.47	0.98
6	21.94	7.51	21.10	6.97	1.04
8	10.93	5.54	11.62	5.07	0.94
10	5.15	4.47	5.46	4.96	0.94
12	1.86	3.75	1.61	3.55	1.15
16	0.46	1.61	0.45	1.59	1.02
24	0.00	0.00	0.00	0.00	.

2. PK parameters and 90% confidence intervals

The arithmetic and geometric means for the PK parameters are shown in Table V-2. PK parameters, AUCT, AUCI, CMAX, LAUCT, LAUCI, and LCMAX for the test and reference products are comparable to each other. Their Test/Reference ratios range 0.97-1.01.

Table V-3 shows the LSMEANS for the test and reference products and the 90% confidence intervals for AUCT, AUCI and CMAX. The LSMEANS are comparable for the test and reference products. The Test/Reference ratios range 0.97-1.02. The 90% confidence intervals for the log-transformed AUCT, AUCI and CMAX are within the acceptable range of 80-125%.

No sequence effect was observed for LAUCT, LAUCI AND LCMAX.

TABLE V-2. ARITHMETIC/GEOMETRIC MEANS AND RATIOS
UNDER FASTING CONDITIONS
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG
MEAN1=TEST; MEAN2=REFERENCE; RMEAN12=MEAN1/MEAN2 RATIO
SD=STANDARD DEVIATION

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	433.58	95.14	428.75	95.08	1.01
AUCT	393.85	99.99	396.62	93.09	0.99
CMAX	144.29	34.61	146.83	29.38	0.98
KE	0.30	0.05	0.31	0.06	0.99
LAUCI	424.53	0.21	420.04	0.20	1.01
LAUCT	382.65	0.24	387.59	0.21	0.99
LCMAX	140.10	0.25	143.69	0.22	0.97
THALF	2.35	0.45	2.36	0.56	1.00
TMAX	0.88	0.32	0.97	0.40	0.91

TABLE V-3. LSMEANS AND 90% CONFIDENCE INTERVALS
UNDER FASTING CONDITIONS
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG
LSM1=TEST; LSM2=REFERENCE; RLSM12=LSM1/LSM2 RATIO
LOWCI12=LOWER 90% CI; UPPCI12=UPPER 90% CI

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	435.75	427.54	1.02	97.97	105.87
AUCT	393.85	396.62	0.99	94.83	103.77
CMAX	144.29	146.83	0.98	92.71	103.83
LAUCI	425.13	418.78	1.02	97.58	105.61
LAUCT	382.65	387.59	0.99	94.26	103.40
LCMAX	140.10	143.69	0.97	91.46	103.94

VI. Formulation and Dissolution Data

1. Formulation

The test formulation is shown in Table VI-1.

Table V-1. Test Formulation

Ingredient	Amount per tablet, mg
Methotrexate,	2.5
Lactose Monohydrate,	
Pregelatinized Starch,	
[illegible]	[illegible]
Magnesium Stearate,	
Total weight	

2. Assay and content uniformity data

Table VI-2 shows the assay and content uniformity for the test and reference products.

Table VI-2. Assay and Content Uniformity

Product	Assay, %	Content Uniformity, % (%CV)
Test: Methotrexate Tablets, 2.5 mg Lot #GA194 Lot size: tablets		101.1 (3.0)
Reference: Methotrexate Sodium Tablets, 2.5 mg Lot #397-336 Exp: 11/97		99.4 (1.9)

3. Dissolution testing

USP23 dissolution method was used. The test and reference products met the USP specifications as shown in Table VI-3. The USP dissolution specifications are shown below:

Medium and Volume	0.1 N HCl; 900 mL
Apparatus and rpm	2 (paddle); 50 rpm
Time	45 min
Tolerances	NLT 75% (Q)

VII. Summary and Comments

1. **Pharmacokinetic and statistical evaluation:** Twenty-six healthy male subjects enrolled and all 26 completed the crossover study. Data from all 26 subjects were used in the pharmacokinetic/statistical evaluation. Peak mean plasma levels for the test and reference products were 128.9 ng/mL at 0.67 hour and 131.6 ng/mL at 0.83 hour, respectively. The LSMEANS are comparable for the test and reference products. The Test/Reference ratios range 0.97-1.02. The 90% confidence intervals for the log-transformed AUCT, AUCI and CMAX are within the acceptable range of 80-125%.

2. **Bioanalytical method validation:** Pre-study and within-study validation data are acceptable.

3. **Dissolution testing:** The test product, lot #GA194, met the USP dissolution specifications.

4. **Drug products:** The assay and content uniformity data for the test and reference products are acceptable. The batch size of the test product was ablets.

5. **Medical events:** A total of two medical events (2 for the reference product involving Subject #23.) were reported. No serious medical events were reported during the study.

VIII. Deficiency

None.

IX. Recommendations

1. The *in vivo* bioequivalence study conducted under fasting conditions by Duramed on its Methotrexate Tablets, 2.5 mg strength, lot #GA194, comparing it to Lederle's Methotrexate Sodium Tablets, 2.5 mg tablet, lot #397-336, has been found acceptable. The study demonstrates that Duramed's Methotrexate Tablets, 2.5 mg strength, is bioequivalent to the reference product, Lederle's Methotrexate Sodium Tablets, 2.5 mg tablet.

2. The USP dissolution testing conducted by Duramed on its Methotrexate Tablets, 2.5 mg strength, lot #GA194, is acceptable.

3. The USP dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of 0.1 N HCl at 37°C using USP 23 Apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

   Not less than 75% of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

The firm should be informed of the recommendations.

/S/

Moo Park, Ph.D.
Chemist, Review Branch III
Division of Bioequivalence

/S/

RD INITIALED RMHATRE
FT INITIALED RMHATRE
Ramakant M. Mhatre, Ph.D.
Team Leader, Review Branch III
Division of Bioequivalence

7/9/97

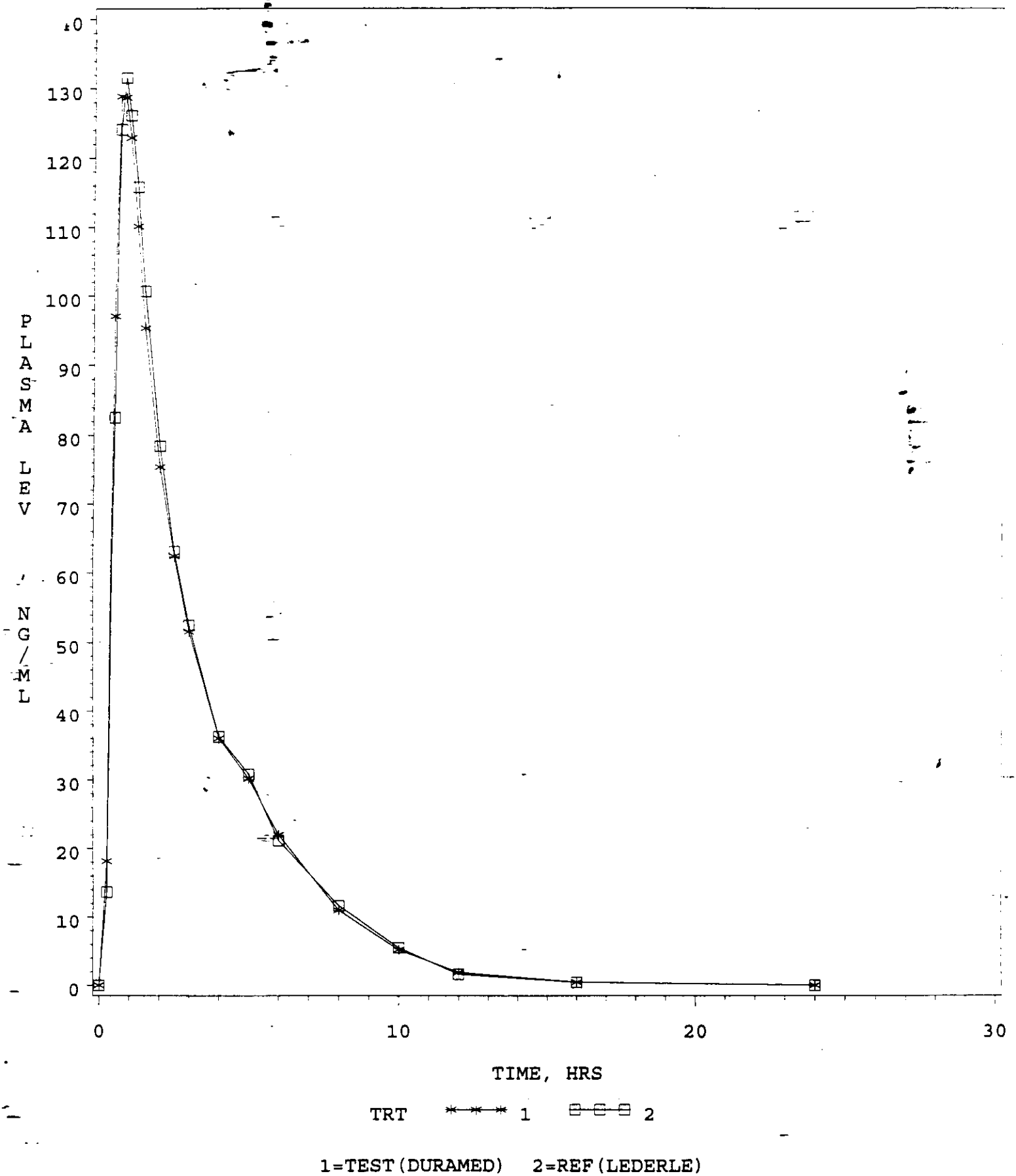
Concur: /S/ Date: 11/13/97

Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence

Table IV-3. *In Vitro* Dissolution Testing Data						
I. General Information						
Drug Product (Generic Name)	Methotrexate Tablets					
Strength	2.5 mg					
ANDA Number	40-233					
Applicant	Duramed					
Reference Drug Product	Lederle's Methotrexate Sodium Tablets, 2.5 mg					
II. USP Method for Dissolution Testing						
Medium and Volume	0.1 N HCl; 900 mL					
Apparatus and rpm	2 (paddle); 50 rpm					
Time	45 min					
Tolerances	NLT 75% (Q)					
Assay Method						
III. Dissolution Data (%)						
Time	Test Product Lot No: GA194 Strength: 2.5 mg No of Units: 12			Reference Product Lot No: 397-336 Strength: 2.5 mg No of Units: 12		
Min	Mean	Range	%CV	Mean	Range	%CV
5	83		8.8	21		14.1
10	94		5.1	48		6.9
15	95		5.2	76		7.3
45	96		4.5	100		2.2

FIG P- . PLASMA METHOTREXATE LEVELS

METHOTREXATE TABLETS, 2.5 MG, ANDA #40-233
UNDER FASTING CONDITIONS
DOSE=2 X 2.5 MG



BIOEQUIVALENCY - Acceptable

ANDA/AADA: 40-233 APPLICANT: Duramed

DRUG PRODUCT: Methotrexate 2.5mg tabs

1. **FASTING STUDY** (STF)
   Clinical: _____
   Analytical: _____
   Strengths: 2.5mg Acceptable
   Outcome: (AC) **IC UN NC**

2. **FOOD STUDY** (STP)
   Clinical: _____
   Analytical: _____
   Strengths: _____
   Outcome: AC IC UN NC

3. **MULTIPLE DOSE STUDY** (STM)
   Clinical: _____
   Analytical: _____
   Strengths: _____
   Outcome: AC IC UN NC

4. **DISSOLUTION DATA** (DIS)
   All Strengths
   Outcome: **AC IC UN NC**

5. **STUDY AMENDMENT** (STA)
   Strengths: _____
   Outcome: AC IC UN NC

6. **WAIVER** (WAI)
   Strengths: _____
   Outcome: AC IC UN NC

7. **DISSOLUTION WAIVER** (DIW)
   Strengths: _____
   Outcome: AC IC UN NC

8. **OTHER** (OTH) _____
   Strengths: _____
   Outcome: AC IC UN NC

9. **OTHER OPTIONS** (less common):
   Strengths: _____

   a. Protocol (PRO)
   b. Protocol Amendment (PRA)
   c. Protocol/Dissolution (PRD)
   d Special Dosage (STS)
   e. Study/Dissolution (STD)
   f. Bio study (STU)

   Outcome: AC IC UN NC

OUTCOME DECISIONS:

AC - Acceptable
NC - No Action
UN - Unacceptable (fatal flaw)
IC - Incomplete

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 40-233

ADMINISTRATIVE DOCUMENTS

APPROVAL SUMMARY PACKAGE

ANDA NUMBER: 40-233

FIRM: Duramed Pharmaceuticals, Inc.

DOSAGE FORM: Tablet

STRENGTHS: 2.5 mg

DRUG: Methotrexate Tablets

CGMP STATEMENT/EIR UPDATED STATUS:
EER status for all facilities listed in Section # 33 of CR # 4 of this ANDA is "Withhold" as of 6-30-98 by J.D. Ambrogia and there is no change in status since then.

BIO STUDY:
Acceptable as of sign off done on 1-16-98.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
MV is not required for the drug product. However, Philadelphia FDA District verified the methods for identification, assay, content uniformity and dissolution submitted in this ANDA.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?
Containers used in the stability studies are identical to those listed in container section.

LABELING:
FPL - acceptable per review completed by T. Watkins on 5-24-99.

STERILIZATION VALIDATION (IF APPLICABLE):
N/A

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?):
Methotrexate Tablets 2.5 mg (used for in-vivo bio studies and in-vitro dissolution studies): Lot # GA 194 (Size: Tablets).

Present status of Referenced DMF:

Referenced for is adequate per last review conducted by Steve Sherken on 12-11-97. No new information is submitted since this last review..

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA SAME PROCESS?)

Bio/stability Batches:

Methotrexate Tablets 2.5 mg: Lot # GA 194 (Size: Tablets).

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?

Production batch sizes post-approval to this ANDA are: Tablets and blets.

Manufacturing process for intended production size batch is same as used for the bio/stability batches.

Mujahid L. Shaikh /S/ 6/7/99
Review Chemist
Division of Chemistry I
OGD/CDER
5-28-99
Steve Sherken for Mike Smela/5/28/99 /S/ 6/7/99

V:\firmsam\duramed\ltrs&rev\40233app.sum

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

ANDA Number: **40-233** Date of Submission: **October 9, 1998**

Applicant's Name: **Duramed Pharmaceuticals, Inc.**

Established Name: **Methotrexate Tablets USP, 2.5 mg**

Labeling Deficiencies:

1. CONTAINER (36s and 100s)

   Satisfactory in final.

2. INSERT

   Due to changes in the labeling of the reference listed drug, please revise your insert as follows:

   a. BOXED WARNING

      Include the following to appear as boxed warnings 8, 9, and 10:

      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. Reaction 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.

b. PRECAUTIONS

i. Carcinogenesis, Mutagenesis, and Impairment of Fertility.

Delete "and" from this subsection title.

ii. Organ System Toxicity-Infection or Immunologic States

Revise the first sentence of paragraph two of this subsection to read as follows:

Potentially fatal opportunistic infections, especially *Pneumocystis carinii* pneumonia, may occur with methotrexate therapy.

iii. Organ System Toxicity-Renal

Include the following to appear immediately after the Pulmonary subsection.

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.

iv. Organ System Toxicity-Skin

Include the following to appear immediately following the Organ System Toxicity-Renal Subsection:

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.

c. ADVERSE REACTIONS

i. Include the following to appear immediately after the Alimentary System subsection:

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

ii. Central Nervous System-Revise the last sentence of this subsection to read as follows:

Following low doses, there have been occasional reports of transient subtle cognitive dysfunction, mood alteration, unusual cranial sensations, leukoencephalopathy, or encephalopathy.

iii. Include the following to appear immediately after the Central Nervous System subsection:

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.

iv. Skin-Revise this subsection to read as follows:

...necrolysis, Stevens-Johnson syndrome, skin necrosis, and exfoliative dermatitis.

v. Urogenital System

A. Revise the first paragraph of this subsection to read as follows:

...dysfunction, vaginal discharge, and gynecomastia; infertility, abortion, fetal defects.

B. Delete "opportunistic infections" from the second paragraph of this subsection.

d. DOSAGE AND ADMINISTRATION

i. Neoplastic Diseases

A. Relocate the last sentence of paragraph one of this subsection to appear as the second paragraph under HANDLING AND DISPOSAL.

B. Include the following to appear as paragraph five of this subsection.

Leukemia: Acute lymphoblastic leukemia in pediatric patients and young adolescents 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.

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

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: **ANDA 40233/000**
Stamp: **23-DEC-1996** Regulatory Due:
Applicant: **DURAMED PHARMS**
5040 LESTER RD
CINCINNATI, OH 45213

Priority:
Org Code: **600**
Action Goal:
District Goal: **23-FEB-1998**
Brand Name:
Established Name: **METHOTREXATE**
Generic Name:
Dosage Form: **TAB (TABLET)**
Strength: **2.5 MG**

FDA Contacts: **ID = 122344** , **Project Manager**
M. SMELA JR (HFD-625) 301-827-5848 , **Team Leader**

Overall Recommendation:

WITHHOLD on 30-JUN-1998 by J. D AMBROGIO (HFD-324) 301-827-0062
WITHHOLD on 08-MAY-1998 by R. WOODS (HFD-324) 301-827-0062

Establishment:

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **06-APR-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE OTHER TESTER**

Establishment:

DMF No:
AADA No:

)504

Profile: **TCM** OAI Status: **NONE**
Last Milestone: **ASSIGNED INSPECTION TO IB**
Milestone Date: **12-APR-1999**

Responsibilities: **FINISHED DOSAGE MANUFACTURER**
FINISHED DOSAGE OTHER TESTER
FINISHED DOSAGE PACKAGER

Establishment:

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **07-APR-1999**
Decision: **ACCEPTABLE**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Reason: **BASED ON PROFILE**

Establishment:

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **06-APR-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE OTHER TESTER**
FINISHED DOSAGE OTHER TESTER

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 40-233

CORRESPONDENCE

DURAmed

The Art of Leadership...
The Science of Change

Duramed Pharmaceuticals, Inc.
5040 Duramed Drive
Cincinnati, Ohio 45213

(513) 731-9900

May 20, 1999

Mr. Douglas L. Sporn
Director, Office of Generic Drugs, CDER
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

[redacted] CORRES
NC to Fax

RE: **ANDA 40-233: Methotrexate Tablets, USP, 2.5 mg**
Subject: **FACSIMILE AMENDMENT**

Dear Mr. Sporn:

Reference is made to your facsimile correspondence dated April 27, 1999 concerning deficiencies in our abbreviated new drug application (ANDA) #40-233 for Methotrexate Tablets, USP. We have noted the deficiencies cited and are amending the application, having responded to all of the deficiencies. For each item we first restate the deficiency then present our response or explanation. As requested, we have included a side-by-side comparison of our proposed labeling with our last submission.

This **Facsimile Amendment** is submitted in one (1) volume and includes two (2) copies, an archival copy and a review copy. In addition, a copy of the response minus the final printed labeling was faxed to the document control room at 301-827-4337.

We certify that a true copy of the technical section as described in 21 CFR 314.94 (d)(5) has been provided to the Food and Drug Administration, Atlanta District Office, Atlanta, Georgia.

Please direct any written communications regarding this ANDA to me at the above address. If you have any questions or require any additional information, please contact Ms. Annette Arlinghaus at (513) 731-9900, by fax at (513) 731-6482, or the undersigned at (513) 458-7274.

Sincerely,

Annette Arlinghaus /for

John R. Rapoza, M.S., R.Ph.
Vice President, Regulatory Affairs

Enclosures: completed Form FDA 356h

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAY 2 1 1999
OGD

DURAmed

FPL

ORIG AMENDMENT

N/AC

Duramed Pharmaceuticals, Inc.
5040 Lester Road
Cincinnati, Ohio 45213

(513) 731-9900
(800) 543-8338

The Art of Leadership...
The Science of Change

October 9, 1998

Mr. Douglas L. Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: **ANDA 40-233: Methotrexate Tablets, USP, 2.5 mg**
Subject: **MAJOR AMENDMENT**

Dear Mr. Sporn:

Reference is made to your facsimile correspondence dated July 18, 1997 concerning deficiencies in our abbreviated new drug application (ANDA) #40-233 for Methotrexate Tablets, USP.

We have noted the deficiencies cited and are amending the application, having responded to all of the deficiencies. For each item we first restate the deficiency then present our response or explanation. As requested, we have included a side-by-side comparison of our proposed labeling with our last submission.

This **Major Amendment** is submitted in one (1) volume and includes two (2) copies, an archival copy and a review copy.

We certify that a true copy of the technical section as described in 21 CFR 314.94 (d)(5) has been provided to the Food and Drug Administration, Atlanta District Office, Atlanta, Georgia.

Please direct any written communications regarding this ANDA to me at the above address. If you have any questions or require any additional information, please contact Ms. Annette Arlinghaus at (513) 731-9900, by fax at (513) 731-6482, or the undersigned at (513) 458-7274.

Sincerely,

Annette Arlinghaus /for

John R. Rapoza, M.S., R.Ph.
Vice President, Regulatory Affairs

OCT 1998

Enclosures: completed Form FDA 356h

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Duramed Pharmaceuticals, Inc.
5040 Lester Road
Cincinnati, Ohio 45213
(513) 731-9900

April 16, 1997

NDA DRUG AMENDMENT

N/AC

Mr. Douglas L. Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 40-233 for Methotrexate Tablets, USP, 2.5 mg

Subject: **AMENDMENT - Addition of 36 count commercial package**

Dear Mr. Sporn:

Reference is made to your Refuse-to-File letter dated February 28, 1997. Our response to item 1 stated that we withdrew the 36 count commercial package due to lack of stability data. The data is now available and we are amending our application to include the 36 count package as a commercial package. The other applicable items specific to this package size were included in the original filing.

This **Amendment,** consisting of a two (2) page updated Stability Report (pages 1074 and 1075 of the original ANDA submission), now includes 1, 2 and 3 month AST, and 3 month RT results for the 36 count commercial package configuration.

This amendment includes two (2) copies, an archival copy and a review copy.

We certify that a true copy of this submission has been provided to the Food and Drug Administration, Atlanta District Office, Atlanta, Georgia.

If you have any questions, please feel free to contact Ms. Annette Arlinghaus or the undersigned by telephone at (513) 731-9900, or by fax at (513) 731-6482.

Sincerely,

John R. Rapoza, M.S., R.Ph.
Vice President, Regulatory Affairs

RECEIVED
APR 18 1997
GENERIC DRUGS

Enclosures: completed FDA 356h
stability tables

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Duramed Pharmaceuticals, Inc.
5040 Lester Road
Cincinnati, Ohio 45213
(513) 731-9900

March 13, 1997

Mr. Jerry Phillips
Director, Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville, MD 20857

RE: ANDA 40-233 for Methotrexate Tablets USP, 2.5 mg

Subject: **Amendment**

Dear Mr. Phillips:

Reference is made to your correspondence dated February 28, 1997 concerning minor administrative deficiencies in our Abbreviated New Drug Application 40-233 for Methotrexate Tablets USP, 2.5 mg. We have noted the deficiencies and are amending our application, having responded to all of the deficiencies. This amendment is formatted such that each deficiency is restated and then followed by our response.

This amendment includes two (2) copies, an archival copy and a review copy.

We certify that a true copy of this submission has been provided to the Food and Drug Administration, Atlanta District Office, Atlanta, Georgia.

If you have any questions, please contact Ms. Annette Arlinghaus or the undersigned by telephone at (513)-731-9900, or by fax at (513)-731-6482.

Sincerely,

John R. Rapoza, M.S., R.Ph.
Vice President, Regulatory Affairs

ANDA 40-233

Duramed Pharmaceuticals, Inc.
Attention: John Repoza
5040 Lester Road
Cincinnati, OH 45213

APR 7

Dear Sir:

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

Reference is also made to our "Refuse to File" letter dated February 28, 1997, and your amendment dated March 13, 1997.

NAME OF DRUG: Methotrexate Tablets USP, 2.5 mg

DATE OF APPLICATION: December 20, 1996

DATE OF RECEIPT: December 23, 1996

DATE ACCEPTABLE FOR FILING: March 14, 1997

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:

Sheila O'Keefe

Project Manager
(301) 594-0370

Sincerely yours,

/S/

Jerry Phillips 4/4/97
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 40-233

Duramed Pharmaceuticals, Inc.
Attention: John Repoza
5040 Lester Road
Cincinnati, OH 45213

FEB 28 '97

Dear Mr. Repoza:

Please refer to your abbreviated new drug application (ANDA) dated December 20, 1996 submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Methotrexate Tablets USP, 2.5 mg.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reasons:

Your stability data is incomplete. Please submit at least three months accelerated stability data on the largest and the smallest container sizes intended for market. The data for the 100 count package size is present, however, the data for the 36 count package is not complete, being comprised of only the initial data and no data for the 30-, 60- and 90-day stations.

Additionally, the dissolution data, as presented, does not include all the data necessary for a complete evaluation by the reviewer. In addition to the individual tablet data, means, range and relative standard deviation (RSD) at each time point and a description of the methodology being used, the dissolution report should also contain the lot numbers being tested, the designations "test preparation" and "reference preparation" are not adequate.

You have failed to completely package your test batch for lot GA194 in containers proposed for marketing. Please refer to the letters to industry from the Director, Office of Generic Drugs, dated November 8, 1991, and August 4, 1993. In addition, we refer you to the Office of Generic Drugs, Policy and Procedure Guide #41-91, dated February 8, 1995. Please provide documentation to confirm that the portion of the test batch packaged in the containers proposed for marketing is representative of the entire

batch. Such documentation should include testing results for in-process or packaged product that demonstrate homogeneity of the manufactured product.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

Within 30 days of the date of this letter you may amend your application to include the above information or request, in writing, an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(a)(3) If you do so, the application shall be filed over protest under 21 CFR 314.101(a)(2). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

Sheila O'Keefe
Project Manager
(301) 594-0370

Sincerely yours,

/S/

Jerry Phillips 2/25/97
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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Duramed Pharmaceuticals, Inc.
5040 Lester Road
Cincinnati, Ohio 45213
(513) 731-9900
(800) 543-8338

December 20, 1996

Mr. Douglas L. Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA for Methotrexate Tablets, USP, 2.5 mg

Dear Mr. Sporn:

Duramed Pharmaceuticals, Inc. (Duramed) submits today an original abbreviated new drug application (ANDA) seeking approval to market Methotrexate Tablets USP, 2.5 mg, that are bioequivalent to the reference drug, Lederle's Methotrexate Sodium Tablets, manufactured by Lederle pursuant to NDA # 08-085.

The facility for manufacturing of this dosage form is located at 2225 Centennial Drive in Gainesville, Georgia.

In accordance with the study protocol, approved by the Office of Generic Drugs (refer to documents included in Section VI), Duramed conducted one definitive *in vivo* bioequivalence study using 2.5 mg tablets.

Methotrexate Tablets, USP, 2.5 mg are stable and a two year expiration dating is requested for all package sizes. The two year expiration dating is supported by accelerated stability testing.

This ANDA is submitted in three (3) volumes. Duramed is filing an archival copy (blue folders) of the application that contains all the information required in the ANDA and a technical review copy (red folders) containing all the information in the archival copy with the exception of the Bioequivalence section. The Bioequivalence section (orange folders) contains the bioequivalence data as well a computer disk, in 3.5" format, containing ASCII files of the measured concentrations of the drug substance and the kinetic parameters for the bioequivalence study.

For more detailed information on the organization of this ANDA, please refer to the "Executive Summary - Organization of the ANDA" which follows this letter.

We certify that a true copy of the technical section described in 21 CFR 314.50 (d)(1), the chemistry, manufacturing, and controls section of this submission, has been provided to the Atlanta District Office of the Food and Drug Administration.

Please direct any written communications regarding this ANDA to me at the above address. If you have any questions or require any additional information, please feel free to contact Ms. Annette Arlinghaus at (513) 731-9900, or me at (513) 458-7294.

Sincerely,

John R. Rapoza, M.S., R.Ph.
Vice President, Regulatory Affairs

enclosures:
-Completed FDA Form 356h
-ANDA Submission