Methotrexate Tablets, USP for oral administration are available in a packaging system designed to facilitate the delivery of methotrexate to the patient. (See BROAD WARNING.)

Methotrexate Tablets USP contain the following inactive ingredients: Lactose, Magnesium stearate, and Color Add. May also contain Corn Starch.

CLINICAL PHARMACOLOGY

Methotrexate inhibits dihydrofolate reductase. Dihydrofolates must be reduced to monohydrofolate to be used in the synthesis of purines and pyrimidines. Methotrexate is a competitive inhibitor of dihydrofolate reductase and in high doses is a noncompetitive inhibitor. Methotrexate is also a potent inhibitor of thymidylate synthetase, the enzyme which catalyzes the conversion of deoxyuridylate to deoxythymidylate. Methotrexate can be metabolized in the liver, with approximately 80% excreted in urine and 20% in feces, without apparent problems. It should be appreciated, however, that the doses used in rheumatoid arthritis are many times greater than those used in the treatment of neoplastic diseases only.

Methotrexate is eliminated from the body by glomerular filtration and active tubular secretion. Methotrexate is also partially metabolized in the liver to 7-hydroxymethotrexate. The aqueous solubility of 7-hydroxymethotrexate is 3 to 5 mg/ml. 7-hydroxymethotrexate is equipotent to methotrexate as an antimetabolite but at concentrations greater than 200 μg/ml is a competitive inhibitor of dihydrofolate reductase.

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Methotrexate has been evaluated in a number of animal studies for carcinogenic potential with mixed results. Although there is evidence that methotrexate causes neoplasms in mice, no evidence of this effect has been observed in rats. Methotrexate has been considered to be unlikely to cause malignant lymphoma in humans; however, there have been instances of malignant lymphoma arising during treatment with low-dose methotrexate. Although no controlled human data exist regarding the risk of neoplasia with methotrexate, it has been observed with methotrexate. Use of methotrexate with penicillins should be avoided. (See CLINICAL PHARMACOLOGY, ADVERSE REACTIONS.)

Geriatric Use: The antineoplastic effect of methotrexate is not significantly altered in geriatric patients. However, the frequency of toxicity increases. Therefore, the patient's age should be considered when choosing a dose for elderly patients. (See DOSAGE AND ADMINISTRATION.)

Drug Interactions: The use of methotrexate with antineoplastic agents should be avoided, except in special circumstances, such as treatment of acute lymphoblastic leukemia. Methotrexate has been observed to increase the toxicity of certain drugs, including vinca alkaloids, daunorubicin, cytarabine, ciclosporine, 13-cis-retinoic acid, and thalidomide. Methotrexate may also interfere with the metabolism of anticonvulsant drugs, leading to increased plasma levels of the anticonvulsant and the potential for toxicity. Concomitant use of methotrexate with such anticonvulsants should be avoided. (See CLINICAL PHARMACOLOGY, ADVERSE REACTIONS.)

The approximate incidences of methotrexate adverse effects in adults are as follows: nausea/vomiting 90%, stomatitis, pneumonitis, fever, leukopenia, thrombocytopenia, hepatotoxicity, and skin rash. The incidence of these adverse reactions in children is similar to that in adults. The onset of these effects is usually within 48-72 hours of the first dose and may proceed to bone marrow suppression as early as 7-10 days, but many of these effects may not occur until the second or third dose. The frequency and severity of these effects increases with dose, with a dose of less than 1 mg/m2 per week producing NCI Grades 1 and 2, whereas a dose of 2-5 mg/m2 per week may produce Grade 3-4 hematological and nonhematological effects. The severity of the hematological effects usually parallels the cumulative dose. The incidence of nonhematological effects should be anticipated, since they are dependent on the dose and the incidence of hematological effects is independent of the dose. The hematological effects usually resolve with discontinuation of the drug and may require granulocyte growth factors.