METHOTREXATE For Cancer (Systemic)

Category

Antineoplastic.

Indications

Note: Bracketed information in the Indications section refers to uses that are not included in U.S. product labeling.

Accepted

Carcinoma, breast (treatment)

Carcinoma, head and neck (treatment)

Carcinoma, lung, non-small cell (treatment) *

Carcinoma, lung, small cell (treatment) * or

Tumors, trophoblastic, gestational (treatment)¾ Methotrexate is indicated for treatment of breast carcinoma 15 , head and neck cancers (epidermoid) 15 , non-small cell lung carcinoma 15 (especially squamous cell types), small cell lung carcinoma 15 , and gestational trophoblastic tumors 15 (gestational choriocarcinoma, chorioadenoma destruens, hydatidiform mole).

[Carcinoma, cervical (treatment)] *

[Carcinoma, ovarian, epithelial (treatment)] *

[Carcinoma, bladder (treatment)]

[Carcinoma, colorectal (treatment)] *

[Carcinoma, esophageal (treatment)] *

[Carcinoma, gastric (treatment)]

[Carcinoma, pancreatic (treatment)] * or

[Carcinoma, penile (treatment)] *¾Methotrexate is indicated for treatment of cervical carcinoma 7, 15 , ovarian carcinoma 15 , bladder carcinoma 15 , colorectal carcinoma 11, 12, 15 , esophageal carcinoma 12, 13, 15, 16 , gastric carcinoma 12, 15, 17 , pancreatic carcinoma 12, 15, 18 , and penile carcinoma 15, 19.

Leukemia, acute lymphocytic (treatment) or

Leukemia, meningeal (prophylaxis and treatment)¾ Methotrexate is indicated for treatment of acute lymphocytic leukemia 15 and prophylaxis and treatment of meningeal leukemia 15.

[Leukemia, acute nonlymphocytic (treatment)] *¾Methotrexate is indicated for treatment of acute nonlymphocytic leukemia 15.

Lymphomas, non-Hodgkin's (treatment)¾Methotrexate is indicated for treatment of non-Hodgkin's lymphomas, including advanced cases of lymphosarcoma (particularly in children) and Burkitt's lymphoma 15.

[Lymphomas, Hodgkin's (treatment)] *¾Methotrexate is indicated for treatment of Hodgkin's disease 9, 12, 15.

Mycosis fungoides (treatment)¾Methotrexate is indicated for treatment of advanced cases of mycosis fungoides.

Osteosarcoma (treatment)¾Methotrexate is indicated in high doses along with leucovorin rescue, in combination with other agents, for treatment of nonmetastatic osteosarcoma in patients who have undergone primary surgical treatment.

[Sarcomas, soft tissue (treatment)] *¾Methotrexate is indicated for treatment of soft tissue sarcomas 12, 15, 20.

[Carcinomatous meningitis (treatment)] *¾Methotrexate is indicated for treatment of carcinomatous menigitis (intrathecal and intraventricular administration) 26, 27, 28, 29, 30, 31 (Evidence rating: IIID).

[Tumors, brain (treatment)] *¾Methotrexate is indicated for treatment of central nervous system (CNS) lymphomas. 34

Note: Although methotrexate has been used for treatment of multiple myeloma, the USP Division of Information Development Hematology-Oncology Advisory Panel believes there is insufficient evidence to support the effectiveness of methotrexate in the treatment of multiple myeloma 32, 33.

Unaccepted

Methotrexate has not shown benefit in the treatment of primary gliomas. 34

* Not included in Canadian product labeling.

Pharmacology

Mechanism of action/Effect:

Methotrexate is an antimetabolite of the folic acid analog type. Methotrexate is cell cycle-specific for the S phase of cell division. Activity is due to inhibition of DNA synthesis, repair, and cellular replication; inhibition occurs as a result of relatively irreversible binding of methotrexate with dihydrofolate reductase, which prevents reduction of dihydrofolate to the active tetrahydrofolate 8.

Growth of rapidly proliferating cells (malignant cells, bone marrow, fetal cells, buccal and intestinal mucosa, cells of the urinary bladder, spermatogonia 3) is affected more severely than growth of most normal tissues and skin.

Other actions/effects:

Also has mild immunosuppressant activity.

Precautions to Consider

Carcinogenicity/Mutagenicity

Secondary malignancies are potential delayed effects of many antineoplastic agents, although it is not clear whether the effect is related to their mutagenic or immunosuppressive action. The effect of dose and duration of therapy is also unknown, although risk seems to increase with long-term use.
Antimetabolites have been shown to be carcinogenic in animals, and may be associated with an increased risk of development of secondary carcinomas in humans, although the risk appears to be less than with alkylating agents.
Carcinogenicity studies with methotrexate in animals have been inconclusive. However, there is evidence that methotrexate causes chromosomal damage to animal somatic cells and human bone marrow cells. 8

Pregnancy/Reproduction

Fertility¾Gonadal suppression, resulting in amenorrhea or azoospermia, may occur in patients taking antineoplastic therapy, especially with the alkylating agents. In general, these effects appear to be related to dose and length of therapy and may be irreversible. Prediction of the degree of testicular or ovarian function impairment is complicated by the common use of combinations of several antineoplastics, which makes it difficult to assess the effects of individual agents. Methotrexate appears to have only a slight effect on gonadal function; however, reversible impairment of fertility, defective oogenesis and spermatogenesis, and menstrual function impairment have been reported.
Pregnancy¾Methotrexate crosses the placenta and has been shown to cause adverse effects in the fetus. Methotrexate is a potent abortifacient.
First trimester: It is usually recommended that use of antineoplastics, especially combination chemotherapy, be avoided whenever possible, especially during the first trimester. Although information is limited because of the relatively few instances of antineoplastic administration during pregnancy, the mutagenic, teratogenic, and carcinogenic potential of these medications must be considered.
Other hazards to the fetus include adverse reactions seen in adults.
In general, use of a contraceptive is recommended during cytotoxic drug therapy.
FDA Pregnancy Category X.

Breast-feeding

Methotrexate is distributed into breast milk; breast-feeding is not recommended while methotrexate is being administered because of the risks to the infant (adverse effects, mutagenicity, carcinogenicity).

Pediatrics

Caution should be used in neonates and infants because of reduced renal and hepatic function.

Geriatrics

Although appropriate studies with methotrexate have not been performed in the geriatric population, caution should be used in the elderly because of possible reduced renal and hepatic functions and reduced folate stores 8.

Dosage adjustment, especially on the basis of renal function status, may be necessary 3.

Dental

The bone marrow depressant effects of methotrexate may result in an increased incidence of microbial infection, delayed healing, and gingival bleeding. Dental work, whenever possible, should be completed prior to initiation of therapy or deferred until blood counts have returned to normal. Patients should be instructed in proper oral hygiene during treatment, including caution in use of regular toothbrushes, dental floss, and toothpicks.
Methotrexate also commonly causes ulcerative stomatitis associated with considerable discomfort.

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.
>> Acyclovir, parenteral

(concurrent administration of intrathecal methotrexate with acyclovir may result in neurological abnormalities; use with caution)

>> Alcohol or

>> Hepatotoxic medications, other (see Appendix II)

(concurrent use may increase the risk of hepatotoxicity)

Allopurinol or

Colchicine or

>> Probenecid or

>> Sulfinpyrazone

(methotrexate may raise the concentration of blood uric acid; dosage adjustment of antigout agents may be necessary to control hyperuricemia and gout; allopurinol may be preferred to prevent or reverse methotrexate-induced hyperuricemia because of risk of uric acid nephropathy with uricosuric antigout agents)

Anticoagulants, coumarin- or indandione-derivative

(methotrexate may increase anticoagulant activity and/or increase the risk of hemorrhage as a result of decreased hepatic synthesis of procoagulant factors and interference with platelet formation)

>> Anti-inflammatory drugs, nonsteroidal (NSAIDs)

(concurrent use of phenylbutazone with methotrexate may increase the risk of agranulocytosis or bone marrow depression and is not recommended; also, phenylbutazone may displace methotrexate from its protein-binding sites and decrease its renal clearance, leading to increased methotrexate plasma concentration and risk of toxicity, especially during high-dose methotrexate infusion therapy. If concurrent use with phenylbutazone cannot be avoided, especially careful monitoring of the patient for plasma methotrexate concentrations 8 or signs of methotrexate toxicity and/or adequacy of renal function is recommended; also, phenylbutazone therapy should be discontinued for 7 to 12 days prior to, and for at least 12 hours [depending on plasma methotrexate concentrations] following, administration of a high-dose methotrexate infusion)
(administration of high-dose methotrexate infusions to patients receiving diflunisal or ketoprofen has resulted in severe and [with ketoprofen] sometimes fatal methotrexate toxicity; a few fatalities have also occurred in patients receiving intermediate-dose methotrexate infusions concurrently with indomethacin, possibly because of decreased methotrexate excretion leading to increased and prolonged methotrexate plasma concentration; however, severe methotrexate toxicity did not occur when ketoprofen was administered 12 hours following completion of the methotrexate infusion. It is recommended that NSAID therapy be discontinued for 24 to 48 hours [for diflunisal] or 12 to 24 hours [for ketoprofen] prior to, and for at least 12 hours [depending on plasma methotrexate concentrations] following, a high-dose methotrexate infusion and that indomethacin be discontinued for 24 to 48 hours prior to, and for at least 12 hours [depending on plasma methotrexate concentrations] following, administration of an intermediate- or high-dose methotrexate infusion)
(although not well documented, the possibility exists that other NSAIDs may also decrease methotrexate excretion and increase its plasma concentration to potentially toxic levels; it is recommended that NSAID therapy be discontinued for 12 to 24 hours [for NSAIDs with a short elimination half-life] to up to 10 days [for piroxicam] prior to, and for at least 12 hours [depending on plasma methotrexate concentrations] following, administration of a high-dose methotrexate infusion)
(severe, sometimes fatal, methotrexate toxicity has also been reported with low to moderate doses in patients receiving diclofenac, indomethacin, naproxen, or phenylbutazone 4, 5 ; it is recommended that use of NSAIDs with low to moderate doses of methotrexate be undertaken with caution, with methotrexate dosage being adjusted by monitoring plasma methotrexate concentrations and/or adequacy of renal function)

>> Asparaginase

(concurrent use may block the effects of methotrexate by inhibiting cell replication; this inhibition of methotrexate's action appears to correlate with suppression of asparagine concentrations. Some studies indicate that administration of asparaginase 9 to 10 days before or within 24 hours after methotrexate

does not produce this inhibition of antineoplastic effect and may reduce the gastrointestinal and hematological effects of methotrexate)

Blood dyscrasia-causing medications (see Appendix II)

(leukopenic and/or thrombocytopenic effects of methotrexate may be increased with concurrent or recent therapy if these medications cause the same effects; dosage adjustment of methotrexate, if necessary, should be based on blood counts)

>> Bone marrow depressants, other (see Appendix II) or

Radiation therapy

(additive bone marrow depression may occur; dosage reduction may be required when two or more bone marrow depressants, including radiation, are used concurrently or consecutively)
(leukoencephalopathy has been reported following intravenous methotrexate administration to patients who have received craniospinal irradiation 8)

Cytarabine

(administration of cytarabine 48 hours before or 10 minutes after initiation of methotrexate therapy may result in a synergistic cytotoxic effect; however, evidence is inconclusive and dosage adjustment based on routine hematologic monitoring is recommended)

Folic acid

(may interfere with the antifolate effects of methotrexate 8)

Neomycin, oral

(may decrease absorption of oral methotrexate)

Penicillins

(concurrent use with methotrexate has resulted in decreased clearance of methotrexate and in methotrexate toxicity; this is thought to be due to competition for renal tubular secretion; patients should be closely monitored; leucovorin doses may need to be increased and administered for longer periods of time 8, 10, 23, 24, 25)

Phenytoin

(concurrent use may result in increased methotrexate toxicity; this is thought to be due to displacement of methotrexate from serum albumin by phenytoin 1, 8, 6)

>> Probenecid

(concurrent use may inhibit renal excretion of methotrexate and result in toxic plasma concentrations; if used concurrently with probenecid, methotrexate dosage should be decreased, the patient observed for signs of toxicity, and/or plasma methotrexate concentrations monitored)

Pyrimethamine or

Triamterene or

Trimethoprim

(concurrent use may rarely increase the toxic effects of methotrexate because of similar folic acid antagonist actions)

>> Salicylates and other weak organic acids

(concurrent use may inhibit renal tubular secretion of methotrexate and result in toxic plasma concentrations; salicylates may also increase plasma concentrations by displacing methotrexate from binding sites; if methotrexate is used concurrently with these medications, the patient should be observed for signs of toxicity and/or methotrexate plasma concentration monitored. In addition, it is recommended that salicylate therapy be discontinued for 24 to 48 hours prior to, and for at least 12 hours [depending on plasma methotrexate concentrations] following, administration of a high-dose methotrexate infusion)

Sulfonamides

(in addition to increased risk of hepatotoxicity that may occur when sulfonamides are used concurrently with other hepatotoxic medications, medications that cause displacement from plasma protein binding may theoretically produce toxic plasma concentrations of methotrexate when used concurrently, although clinical significance has not been established)

Theophylline

(methotrexate may decrease theophylline clearance. Monitoring of serum theophylline concentrations is recommended when it is used concurrently with methotrexate 8, 21, 22)

Vaccines, killed virus

(because normal defense mechanisms may be suppressed by methotrexate therapy, the patient's antibody response to the vaccine may be decreased. The interval between discontinuation of medications that cause immunosuppression and restoration of the patient's ability to respond to the vaccine depends on the intensity and type of immunosuppression-causing medication used, the underlying disease, and other factors; estimates vary from 3 months to 1 year)

>> Vaccines, live virus

(because normal defense mechanisms may be suppressed by methotrexate therapy, concurrent use with a live virus vaccine may potentiate the replication of the vaccine virus, may increase the side/adverse effects of the vaccine virus, and/or may decrease the patient's antibody response to the

vaccine; immunization of these patients should be undertaken only with extreme caution after careful review of the patient's hematologic status and only with the knowledge and consent of the physician managing the methotrexate therapy. The interval between discontinuation of medications that cause immunosuppression and restoration of the patient's ability to respond to the vaccine depends on the intensity and type of immunosuppression-causing medication used, the underlying disease, and other factors; estimates vary from 3 months to 1 year. Patients with leukemia in remission should not receive live virus vaccine until at least 3 months after their last chemotherapy. Immunization with oral poliovirus vaccine should also be postponed in persons in close contact with the patient, especially family members)

Laboratory value alterations

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):
With diagnostic test results

Assay for folate

(methotrexate may inhibit the organism used in the assay and interfere with detection of folic acid deficiency)

With physiology/laboratory test values

Isocitric acid dehydrogenase (ICD)

(values may be increased, indicating hepatotoxicity)

Serum aspartate aminotransferase (AST [SGOT])

(values may be increased transiently during high-dose therapy)

Uric acid concentrations in blood and urine

(may be increased)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).
Except under special circumstances, this medication should not be used when the following medical problem exists

>> Immunodeficiency 8

Risk-benefit should be considered when the following medical problems exist

Aciduria (urine pH less than 7) or

>> Ascites or

Dehydration or

Gastrointestinal obstruction or

>> Pleural or peritoneal effusions or

>> Renal function impairment

(risk of methotrexate toxicity is increased because elimination of methotrexate may be impaired and accumulation may occur; even small doses may lead to severe myelosuppression and mucositis; larger doses and/or increased duration of leucovorin treatment, if used, may be necessary, along with careful monitoring of methotrexate concentrations 2)
(a lower dosage of methotrexate and careful monitoring of plasma or serum methotrexate concentrations are recommended for patients with impaired renal function)

>> Bone marrow depression

>> Chickenpox, existing or recent (including recent exposure) or

>> Herpes zoster

(risk of severe generalized disease)

Gout, history of or

Urate renal stones, history of

(risk of hyperuricemia)

>> Hepatic function impairment

>> Infection

>> Mucositis, oral

Nausea and vomiting

(inadequate hydration secondary to severe nausea and vomiting may result in increased methotrexate toxicity)

>> Peptic ulcer

Sensitivity to methotrexate 8

>> Ulcerative colitis

>> Caution should be used also in patients who have had previous cytotoxic drug therapy and radiation therapy, and in cases of general debility.

Patient monitoring

The following are especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; >> = major clinical significance):
>> Blood urea nitrogen (BUN) concentrations and

Creatinine clearance and/or

>> Serum creatinine concentrations

(recommended prior to initiation of therapy and at periodic intervals during therapy; frequency varies according to clinical state, agent, dose, and other agents being used concurrently)

Bone marrow aspiration studies and

Liver biopsy

(may be useful during high-dose or long-term therapy or if hematologic or hepatic function test results are abnormal; also recommended in patients who have received a cumulative dose of 1500 mg 3, 8)

Examination of patient's mouth for ulceration

(recommended before administration of each dose)

>> Hematocrit or hemoglobin and

>> Platelet count and

>> Total and, if appropriate, differential leukocyte count

(determinations recommended prior to initiation of therapy and at periodic intervals during therapy; frequency varies according to clinical state, agent, dose, and other agents being used concurrently)

>> Serum alanine aminotransferase (ALT [SGPT]) and

>> Serum aspartate aminotransferase (AST [SGOT]) and

>> Serum lactate dehydrogenase (LDH)

(determinations recommended prior to initiation of therapy and at periodic intervals during therapy; frequency varies according to clinical state, agent, dose, and other agents being used concurrently)

>> Serum bilirubin concentrations and

Serum uric acid concentrations

(recommended prior to initiation of therapy and at periodic intervals during therapy; frequency varies according to clinical state, agent, dose, and other agents being used concurrently)

For patients receiving high-dose methotrexate

>> Creatinine clearance determinations

(recommended prior to initiation of high-dose methotrexate with leucovorin rescue therapy or if serum creatinine concentrations increase by 50% or more)

>> Plasma or serum methotrexate concentrations

(recommended by some clinicians every 12 to 24 hours after high-dose methotrexate administration to determine dose and duration of leucovorin treatment needed to maintain rescue. May aid in identifying patients with delayed methotrexate clearance; toxicity appears to be related at least as much to the length of time that methotrexate concentrations are elevated as to the peak concentrations achieved. In general, monitoring should continue until concentrations are less than 5 ´ 10 -8 Molar [M])

>> Serum creatinine concentrations

(recommended prior to and every 24 hours after each methotrexate dose, until plasma or serum methotrexate concentrations are less than 5 ´ 10 -8 M, to detect developing renal function impairment and predict methotrexate toxicity. An increase of greater than 50% over the pretreatment concentration at 24 hours is associated with severe renal toxicity)

>> Urine pH determinations

(recommended prior to each dose of high-dose methotrexate therapy and about every 6 hours throughout leucovorin rescue, until plasma or serum methotrexate concentrations are less than 5 ´ 10 -8 M, to ensure that pH remains greater than 7, so as to minimize the risk of methotrexate nephropathy due to precipitation of methotrexate or its metabolites in the urine)

Side/Adverse Effects

Note: Many "side effects" of antineoplastic therapy are unavoidable and represent the medication's pharmacologic action. Some of these (for example, leukopenia and thrombocytopenia) are actually used as parameters to aid in individual dosage titration.
Incidence and severity of side effects, particularly hepatotoxicity, appear to be related to dosage frequency and duration of methotrexate therapy. Toxicity tends to occur less frequently and be less severe with a total dose administered as intermittent weekly dosage than with prolonged daily dosage.
The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Those indicating need for medical attention

Incidence more frequent

Gastrointestinal ulceration and bleeding, enteritis, or intestinal perforation, which may be fatal (black, tarry stools; bloody vomit; diarrhea); stomach pain); leukopenia, bacterial infection, or septicemia fever or chills); cough or hoarseness); lower back or side pain); painful or difficult urination)¾usually asymptomatic; thrombocytopenia unusual bleeding or bruising); black, tarry stools); blood in urine or stools); pinpoint red spots on skin)¾usually asymptomatic; stomatitis, ulcerative sores in mouth and on lips)

Note: With development of leukopenia and thrombocytopenia, the nadir of the leukocyte and platelet counts occurs after 7 to 10 days, with recovery 7 days later.

Incidence more frequent (with high-dose therapy)

Renal failure, azotemia, hyperuricemia, or severe nephropathy (blood in urine; joint pain; swelling of feet or lower legs); severe acute methotrexate toxicity, cutaneous vasculitis, or reactivation of sunburn or increased erythematous response to ultraviolet therapy reddening of skin)

Note: Hyperuricemia and uric acid nephropathy occur most commonly during initial treatment of patients with leukemia or lymphoma, as a result of rapid cell breakdown which leads to elevated serum uric acid concentrations. With high-dose methotrexate therapy, symptoms resembling uric acid nephropathy may also be due to renal tubular damage resulting from precipitation of methotrexate or metabolites in the urine.

Incidence less frequent, more frequent with prolonged, daily therapy

Hepatotoxicity, including liver atrophy, necrosis, cirrhosis, fatty changes, periportal fibrosis dark urine); yellow eyes or skin); pneumonitis, potentially fatal 8 , or pulmonary fibrosis (cough; shortness of breath)
Incidence less frequent, more frequent with intrathecal or prolonged high-dose administration

Central nervous system (CNS) effects, increased cerebrospinal fluid pressure, leukoencephalopathy, demyelination, or chemical arachnoiditis (back pain; blurred vision; confusion; convulsions 8; dizziness; drowsiness; fever; headache; unusual tiredness or weakness)
Those indicating need for medical attention only if they continue or are bothersome

Incidence more frequent

Loss of appetite; nausea or vomiting
Incidence less frequent

Acne; boils; pale skin; skin rash or itching
Those not indicating need for medical attention

Incidence less frequent

Alopecia (loss of hair)
Those indicating need for medical attention if they occur after medication is discontinued

CNS toxicity (encephalopathy, especially after intrathecal administration, or CNS leukemia) (back pain; blurred vision; confusion; convulsions; dizziness; drowsiness; fever; headache; unusual tiredness or weakness)

Overdose

For specific information on the agents used in the management of methotrexate overdose, see: Leucovorin (Systemic) .
For more information on the management of overdose or unintentional ingestion, contact a Poison Control Center (see Poison Control Center Listing).

Treatment of overdose

Leucovorin should be administered as soon as possible following accidental methotrexate overdosage. The efficacy of leucovorin in reducing methotrexate toxicity decreases as the time between methotrexate administration and the initiation of leucovorin therapy increases 8.

Specific treatment¾Preventing precipitation of methotrexate and metabolites in renal tubules by systemic hydration and urinary alkalization 8.

High dose leucovorin therapy, alkaline diuresis, rapid cerebrospinal fluid drainage, and ventriculolumbar perfusion may be necessary for treating intrathecal overdosage 8.

Monitoring¾Monitoring of serum methotrexate concentration is necessary to determine the required dose and duration of treatment with leucovorin 8.

Supportive care¾Intensive systemic supportive care is necessary following intrathecal overdose 8.

Patients in whom intentional overdose is confirmed or suspected should be referred for psychiatric consultation.

Note: Dialysis is of limited value in the treatment of overdose 8.

Patient Consultation

As an aid to patient consultation, refer to Advice for the Patient, Methotrexate¾For Cancer (Systemic) .
In providing consultation, consider emphasizing the following selected information (>> = major clinical significance):
Before using this medication

>> Conditions affecting use, especially:

Sensitivity to methotrexate
Pregnancy¾Use not recommended because of mutagenic, teratogenic, and carcinogenic potential; advisability of using contraception; telling physician immediately if pregnancy is suspected
Breast-feeding¾Not recommended because of risk of serious side effects
Use in children¾Newborns and other infants may be more sensitive to effects
Use in the elderly¾Side/adverse effects may be more frequent

Other medications, especially acyclovir, alcohol or other hepatotoxic medications, asparaginase, live virus vaccines, nonsteroidal anti-inflammatory drugs (NSAIDs), other bone marrow depressants, previous cytotoxic drug therapy or radiation therapy, probenecid, sulfinpyrazone, or salicylates
Other medical problems, especially chickenpox, herpes zoster, hepatic function impairment, renal function impairment, infection, oral mucositis, peptic ulcer, or ulcerative colitis
Proper use of this medication

>> Importance of not taking more or less medication than the amount prescribed

Caution in taking combination therapy; taking each medication at the right time

Importance of ample fluid intake and subsequent increase in urine output to prevent nephrotoxicity and aid in excretion of uric acid

>> Frequency of nausea and vomiting; importance of continuing medication despite stomach upset

Checking with physician if vomiting occurs shortly after dose is taken

>> Proper dosing
Missed dose: Not taking at all; not doubling doses
>> Proper storage
Precautions while using this medication

>> Importance of close monitoring by physician

>> Avoiding alcoholic beverages, which may increase hepatotoxicity

Possible photosensitivity reactions; avoiding too much unprotected exposure to sun or overuse of sunlamp

>> Avoiding salicylate-containing products and NSAIDs, which may increase toxicity

>> Avoiding immunizations unless approved by physician; other persons in patient's household should avoid immunizations with oral poliovirus vaccine; avoiding other persons who have taken oral poliovirus vaccine or wearing a protective mask that covers nose and mouth

Caution if bone marrow depression occurs

>> Avoiding exposure to persons with infections, especially during periods of low blood counts; checking with physician immediately if fever or chills, cough or hoarseness, lower back or side pain, or painful or difficult urination occurs

>> Checking with physician immediately if unusual bleeding or bruising; black, tarry stools; blood in urine or stools; or pinpoint red spots on skin occur

Caution in use of regular toothbrush, dental floss, or toothpick; physician, dentist, or nurse may suggest alternatives; checking with physician before having dental work done

Not touching eyes or inside of nose unless hands are washed immediately before

Using caution to avoid accidental cuts with use of sharp objects such as safety razor or fingernail or toenail cutters

Avoiding contact sports or other situations where bruising or injury could occur

Side/adverse effects

May cause adverse effects such as blood problems; stomach, kidney, or liver problems; or cancer; importance of discussing possible effects with physician

Signs of potential side effects, especially gastrointestinal ulceration and bleeding, enteritis, intestinal perforation, leukopenia, bacterial infection, septicemia, thrombocytopenia, ulcerative stomatitis, renal failure, azotemia, hyperuricemia, severe nephropathy, severe acute methotrexate toxicity, cutaneous vasculitis, reactivation of sunburn or reaction to ultraviolet light, hepatotoxicity, pneumonitis, pulmonary fibrosis, and CNS effects

Physician or nurse can help in dealing with side effects

Possibility of hair loss; normal hair growth should resume after treatment has ended

General Dosing Information

Patients receiving methotrexate should be under supervision of a physician experienced in antineoplastic chemotherapy.
A variety of dosage schedules and regimens of methotrexate, alone or in combination with other antitumor agents, are used. The prescriber may consult the medical literature as well as the manufacturer's literature in choosing a specific dosage.
Dosage must be adjusted to meet the individual requirements of each patient, based on clinical response and appearance or severity of toxicity.
In general, use of intermittent courses of methotrexate is associated with less risk of serious toxicity than prolonged, daily dosage.
A significant amount of methotrexate passes into systemic circulation after intrathecal administration and may produce toxic levels in patients also receiving systemic methotrexate therapy; an adjustment in systemic dosage may be necessary.
Development of uric acid nephropathy in patients with leukemia or lymphoma may be prevented by adequate oral hydration and, in some cases, administration of allopurinol. Alkalinization of urine may be necessary if serum uric acid concentrations are elevated.
If severe bone marrow depression occurs, withdrawal of methotrexate may be necessary 8.

However, in some patients with acute leukemia, methotrexate may be administered despite the presence of thrombocytopenia and bleeding; stoppage of bleeding and increase in platelet count have occurred during treatment in some cases and platelet transfusions may be useful in others.
Special precautions are recommended in patients who develop thrombocytopenia as a result of administration of methotrexate. These may include extreme care in performing invasive procedures; regular inspection of intravenous sites, skin (including perirectal area), and mucous membrane surfaces for signs of bleeding or bruising; limiting frequency of venipuncture and avoiding intramuscular

injections; testing urine, emesis, stool, and secretions for occult blood; care in use of regular toothbrushes, dental floss, toothpicks, safety razors, and fingernail and toenail cutters; avoiding constipation; and using caution to prevent falls and other injuries. Such patients should avoid alcohol and any aspirin intake because of the risk of gastrointestinal bleeding. Platelet transfusions may be required.
Patients who develop leukopenia should be observed carefully for signs of infection. Antibiotic support may be required. In neutropenic patients who develop fever, broad-spectrum antibiotic coverage should be initiated empirically, pending bacterial cultures and appropriate diagnostic tests.
It is recommended that methotrexate therapy be interrupted if diarrhea or ulcerative stomatitis occurs, because of the risk of hemorrhagic enteritis and fatal intestinal perforation 8.

It is recommended that methotrexate therapy be interrupted if pulmonary symptoms (especially a dry, unproductive cough) occur, because of the risk of potentially irreversible pulmonary toxicity 8.

For use in high-dose methotrexate therapy

Because of its ability to bypass the effects of methotrexate, leucovorin calcium (folinic acid, citrovorum factor) is administered as a "rescue" from the hematologic and gastrointestinal effects of high-dosage methotrexate.
High-dose methotrexate administration should not be initiated unless leucovorin is physically present and ready to be administered, since rescue is critical.
Methotrexate administration should not be initiated unless creatinine clearance is greater than 60 mL per minute and serum creatinine concentrations are normal. If renal function impairment develops during therapy, methotrexate should be withdrawn until creatinine clearance improves to acceptable levels 8.

Methotrexate administration also should not be initiated if:
¾White blood cell count is less than 1500 per microliter
¾Neutrophil count is less than 200 per microliter
¾Platelet count is less than 75,000 per microliter
¾Bilirubin is greater than 1.2 mg per dL
¾Alanine aminotransferase (ALT [SGPT]) values are greater than 450 units 8

Methotrexate administration also should be delayed until healing of stomatitis is evident and until after complete drainage of persistent pleural effusions 8.

A variety of dosage schedules of leucovorin in combination with high-dose methotrexate have been used. The prescriber should consult the medical literature in choosing a specific dosage. Alkalinization of urine (with bicarbonate and/or acetazolamide) and intravenous hydration (1000 mL per square meter of body surface area over 6 hours prior to beginning the methotrexate infusion and 3000 mL per square meter of body surface area per day during the methotrexate infusion and for 2 days after the infusion is completed 8) are also important to prevent renal toxicity caused by methotrexate and/or its metabolites.
Administration of leucovorin should be consecutive to rather than simultaneous with methotrexate administration so as not to interfere with methotrexate's antineoplastic effects.
In general, it is recommended that the first dose of leucovorin be administered 24 hours after a high-dose methotrexate infusion is started (within 1 hour of an overdose), in a dosage to produce blood concentrations equal to or greater than methotrexate blood concentrations (leucovorin in a dose of 15

to 25 mg per square meter of body surface area produces peak plasma concentrations of approximately 1 micromolar or 1 ´ 10 -6 M). Duration of leucovorin administration varies with the dosage of methotrexate and plasma concentrations achieved (including rate of elimination); in general, leucovorin administration is continued until methotrexate concentrations fall to less than 5 ´ 10 -8 M.
A larger dose and/or longer duration of leucovorin treatment may be required in patients with aciduria, ascites, dehydration, gastrointestinal obstruction, renal function impairment, or pleural or peritoneal effusions because excretion of methotrexate is slowed and the length of time for plasma methotrexate concentrations to decrease to nontoxic levels (< 5 ´ 10 -8 M) is increased. It is recommended that duration of leucovorin administration in these patients be based on determination of plasma methotrexate concentrations.

For parenteral use

Methotrexate may be administered intramuscularly, intravenously (rapid or continuous infusion), intrathecally, intra-arterially, or intraventricularly 8.

Caution is recommended in making sure that the appropriate diluent for the intended route of administration is used when preparing methotrexate for administration.

Safety considerations for handling this medication

There is limited but increasing evidence and concern that personnel involved in preparation and administration of parenteral antineoplastics may be at some risk because of the potential mutagenicity, teratogenicity, and/or carcinogenicity of these agents, although the actual risk is unknown. USP advisory panels recommend cautious handling both in preparation and disposal of antineoplastic agents. Precautions that have been suggested include:
· Use of a biological containment cabinet during reconstitution and dilution of parenteral medications and wearing of disposable surgical gloves and masks.
· Use of proper technique to prevent contamination of the medication, work area, and operator during transfer between containers (including proper training of personnel in this technique).
· Cautious and proper disposal of needles, syringes, vials, ampuls, and unused medication.A number of medical centers have developed detailed guidelines for handling of antineoplastic agents.

Combination chemotherapy

Methotrexate may be used in combination with other agents in various regimens. As a result, incidence and/or severity of side effects may be altered and different dosages (usually reduced) may be used. For example, methotrexate is part of the following chemotherapeutic combinations (some commonly used acronyms are in parentheses):
¾cyclophosphamide, doxorubicin, methotrexate, and procarbazine (CAMP).
¾cyclophosphamide, methotrexate, and fluorouracil (CMF).
¾cyclophosphamide, methotrexate, fluorouracil, vincristine, and prednisone (CMFVP).For specific dosages and schedules, consult the literature. For information regarding each agent, consult the individual monographs.

Oral Dosage Forms

Note: Bracketed uses in the Dosage Forms section refer to categories of use and/or indications that are not included in U.S. product labeling.

METHOTREXATE TABLETS USP

Usual adult dose

Choriocarcinoma or
Chorioadenoma destruens or
Hydatidiform mole¾
Oral, 15 to 30 mg per day for five days, the course being repeated three to five times, with one to two weeks between courses. Usually, one or two courses are given after normalization of urinary human chorionic gonadotropin (HCG) concentrations. 8

Acute lymphocytic leukemia¾
Induction: Oral, 3.3 mg per square meter of body surface area per day in combination with prednisone or other agents 8.

Maintenance: Oral, 30 mg per square meter of body surface area per week in two divided doses 8.

Burkitt's lymphoma¾
Stages I-II: Oral, 10 to 25 mg per day for four to eight days, the course being repeated several times, with seven to ten days between courses 8.

Stage III: Oral, as for Stage I-II, in combination with other agents 8.

Lymphosarcoma (Stage III)¾
Oral, 625 mcg (0.625 mg) to 2.5 mg per kg of body weight per day 8.

Mycosis fungoides¾
Oral, 2.5 to 10 mg a day for weeks or months 8.

Carcinoma, breast or
Carcinoma, head and neck or
Carcinoma, lung, non-small cell * or
Carcinoma, lung, small cell * or
[Carcinoma, cervical] * or
[Carcinoma, ovarian, epithelial] * or
[Carcinoma, bladder] or
[Carcinoma, colorectal] * or
[Carcinoma, esophageal] * or
[Carcinoma, gastric] or
[Carcinoma, pancreatic] * or
[Carcinoma, penile] * or
[Leukemia, acute nonlymphocytic] * or
[Lymphomas, Hodgkin's] * or
[Sarcomas, soft tissue] *¾
Consult medical literature or manufacturer's literature for specific dosage.

Usual pediatric dose

Antineoplastic¾
Oral, 20 to 40 mg per square meter of body surface area, once a week 2.

Strength(s) usually available

U.S.¾2.5 mg (Rx) [Generic] (lactose) (magnesium stearate) (pregelatinized starch)

Canada¾2.5 mg (Rx) [Generic]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a well-closed container. Protect from light.

Auxiliary labeling:

· Avoid alcoholic beverages.
· Do not take other medicines without advice from your doctor.
· Avoid overexposure to sun.

Parenteral Dosage Forms

Note: Bracketed uses in the Dosage Forms section refer to categories of use and/or indications that are not included in U.S. product labeling.
The dosing and strengths of dosage forms available are expressed in terms of methotrexate base.

METHOTREXATE SODIUM INJECTION USP

Usual adult dose

Choriocarcinoma or
Chorioadenoma destruens or
Hydatidiform mole¾
Intramuscular, 15 to 30 mg (base) per day for five days, the course being repeated three to five times with one to two weeks between courses. Usually, one or two courses are given after normalization of urinary human chorionic gonadotropin (HCG) concentrations. 8

Acute lymphocytic leukemia¾
Induction¾
Intravenous or intramuscular, 3.3 mg (base) per square meter of body surface area per day in combination with prednisone or other agents 8.

Maintenance¾
Intramuscular, 30 mg (base) per square meter of body surface area per week in two divided doses 8 ; or

Intravenous, 2.5 mg (base) per kg of body weight every fourteen days 8.

Osteosarcoma¾
Intravenous infusion (over four hours), 12 grams (base) per square meter of body surface area, followed by leucovorin rescue (usually 15 mg orally every six hours for ten doses starting at twenty-four hours after the methotrexate infusion is started), on weeks 4, 5, 6, 7, 11, 12, 15, 16, 29, 30, 44, and 45 after surgery on a combination chemotherapy schedule that also includes doxorubicin, cisplatin, bleomycin, cyclophosphamide, and dactinomycin. The dose may be increased, if necessary, to 15 grams (base) per square meter of body surface area to achieve a peak serum methotrexate concentration of 1´10-3 M per liter. 8

Note: High-dose methotrexate administration should not be initiated unless leucovorin is physically present and ready to be administered, since rescue is critical.
If the patient is vomiting or cannot take oral medication, leucovorin may be administered intravenously or intramuscularly at the same dose as the oral dose 8.

Mycosis fungoides¾
Intramuscular, 50 mg (base) once a week or 25 mg (base) two times a week 8.

Carcinoma, breast or
Carcinoma, head and neck or
Carcinoma, lung, non-small cell * or
Carcinoma, lung, small cell * or
[Carcinoma, cervical] * or
[Carcinoma, ovarian, epithelial] * or
[Carcinoma, bladder] or
[Carcinoma, colorectal] * or
[Carcinoma, esophageal] * or
[Carcinoma, gastric] or
[Carcinoma, pancreatic] * or
[Carcinoma, penile] * or
[Leukemia, acute nonlymphocytic] * or
[Lymphomas, Hodgkin's] * or
[Sarcomas, soft tissue] *¾
Consult medical literature or manufacturer's literature for specific dosage.

Usual pediatric dose

Antineoplastic¾
Intramuscular, 20 to 40 mg (base) per square meter of body surface area, once a week 2.

Strength(s) usually available

U.S.¾25 mg (base) per mL (Rx) [Generic] (with and without preservative)

Canada¾2.5 mg (base) per mL (Rx) [Generic] (with and without preservative)

10 mg (base) per mL (Rx) [Generic] (without preservative)

25 mg (base) per mL (Rx) [Generic] (with and without preservative)

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by the manufacturer. Protect from light.

Preparation of dosage form:

Methotrexate Sodium Injection USP may be further diluted with an appropriate preservative-free medium such as 0.9% sodium chloride injection or 5% dextrose injection.

Stability:

If stored for 24 hours at a temperature of 21 to 25 °C (70 to 77 °F), a diluted solution of methotrexate sodium injection maintains 90% of its labeled potency. However, preservative-free solutions should be diluted immediately prior to use and any unused portion discarded 8.

METHOTREXATE SODIUM FOR INJECTION USP

Usual adult dose

Meningeal leukemia¾
Induction: Intrathecal, 12 mg (base) every two to five days until the cell count of the cerebrospinal fluid (CSF) returns to normal 8.

Prophylaxis: Intrathecal, 12 mg (base) at an interval determined by consultation of the medical literature 8.

Choriocarcinoma or
Chorioadenoma destruens or
Hydatidiform mole¾
Intramuscular, 15 to 30 mg (base) per day for five days, the course being repeated three to five times, with one to two weeks between courses. Usually, one or two courses are given after normalization of urinary human chorionic gonadotropin (HCG) concentrations. 8

Acute lymphocytic leukemia¾
Induction¾
Intravenous or intramuscular, 3.3 mg (base) per square meter of body surface area per day in combination with prednisone or other agents 8.

Maintenance¾
Intramuscular, 30 mg (base) per square meter of body surface area per week in two divided doses 8 ; or
Intravenous, 2.5 mg (base) per kg of body weight every fourteen days 8.

Osteosarcoma¾

Intravenous infusion (over four hours), 12 grams (base) per square meter of body surface area, followed by leucovorin rescue (usually 15 mg orally every six hours for ten doses starting at twenty-four hours after the methotrexate infusion is started), on weeks 4, 5, 6, 7, 11, 12, 15, 16, 29, 30, 44, and 45 after surgery on a combination chemotherapy schedule that also includes doxorubicin, cisplatin, bleomycin, cyclophosphamide, and dactinomycin. The dose may be increased, if necessary, to 15 grams (base) per square meter of body surface area to achieve a peak serum methotrexate concentration of 1´10-3 M per liter. 8

Note: High-dose methotrexate administration should not be initiated unless leucovorin is physically present and ready to be administered, since rescue is critical.
If the patient is vomiting or cannot take oral medication, leucovorin may be administered intravenously or intramuscularly in the same dose as the oral dose 8.

Mycosis fungoides¾
Intramuscular, 50 mg (base) once a week or 25 mg (base) two times a week 8.

[Carcinomatous meningitis] *¾
Intrathecal or intraventricular; consult medical literature or manufacturer's literature for specific dosage.
Carcinoma, breast or
Carcinoma, head and neck or
Carcinoma, lung, non-small cell * or
Carcinoma, lung, small cell * or
[Carcinoma, cervical] * or
[Carcinoma, ovarian, epithelial] * or
[Carcinoma, bladder] or
[Carcinoma, colorectal] * or
[Carcinoma, esophageal] * or
[Carcinoma, gastric] or
[Carcinoma, pancreatic] * or
[Carcinoma, penile] * or
[Leukemia, acute nonlymphocytic] * or
[Lymphomas, Hodgkin's] * or
[Sarcomas, soft tissue] *¾
Consult medical literature or manufacturer's literature for specific dosage.

Usual pediatric dose

Meningeal leukemia¾
For children up to 1 year of age: Intrathecal, 6 mg (base) every two to five days until the cell count of the CSF returns to normal 8.

For children 1 year of age: Intrathecal, 8 mg (base) every two to five days until the cell count of the CSF returns to normal 8.

For children 2 years of age: Intrathecal, 10 mg (base) every two to five days until the cell count of the CSF returns to normal 8.

For children 3 years of age and over: Intrathecal, 12 mg (base) every two to five days until the cell count of the CSF returns to normal 8.

Antineoplastic, other¾
Intramuscular, 20 to 40 mg (base) per square meter of body surface area, once a week 2.

Size(s) usually available:

U.S.¾20 mg (base) (Rx) [Generic] (without preservative)

1 gram (base) (Rx) [Generic] (without preservative)

Canada¾20 mg (base) (Rx) [Generic] (without preservative)

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Protect from light.

Preparation of dosage form:

For intrathecal use, methotrexate sodium for injection (containing no preservative) is recommended. It must be reconstituted immediately prior to use with an appropriate volume of a sterile, preservative-free medium such as 0.9% sodium chloride injection to yield a solution containing 1 mg (base) per mL.
For intravenous or intramuscular use, the 20-mg vial of methotrexate sodium for injection is diluted with an appropriate volume of a sterile, preservative-free medium, such as 5% dextrose injection or 0.9% sodium chloride injection, to yield a solution containing not more than 25 mg (base) per mL. The 1-gram vial should be diluted with 19.4 mL of 5% dextrose injection or 0.9% sodium chloride injection to yield a solution containing 50 mg (base) per mL. For high dose intravenous use, methotrexate sodium for injection should only be diluted in 5% dextrose injection 8.

Stability:

Solutions without preservative should be freshly reconstituted immediately prior to each dose; any unused portion should be discarded.