Methotrexate: Drug information

(For additional information see "Methotrexate: Patient drug information" and see "Methotrexate: Pediatric drug information")

For abbreviations and symbols that may be used in Lexicomp (show table)

Special Alerts

Levetiracetam and Methotrexate Safety Alert October 2016

Health Canada has carried out a safety review regarding a potential drug interaction between levetiracetam and methotrexate. Health Canada's review concluded that levetiracetam and methotrexate coadministration may lead to higher amounts of serum methotrexate, which may cause serious adverse events, including acute kidney failure. Product labeling now recommends careful monitoring of levetiracetam and methotrexate serum levels during coadministration.

Further information can be found at http://www.hc-sc.gc.ca/dhp-mps/medeff/reviews-examens/levetiracetam-eng.php.

ALERT: US Boxed Warning

Intrathecal and high-dose therapy:

Use only preservative-free methotrexate formulations and diluents for intrathecal and high-dose therapy. Do NOT use formulations or diluents containing preservatives for intrathecal and high-dose therapy because they contain benzyl alcohol.

Appropriate use:

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, skin, and kidney toxicities. Patients should be informed by their physician of the risks involved and be under a physician's care throughout therapy.

The use of methotrexate high-dose regimens recommended for osteosarcoma requires meticulous care. High-dose regimens of methotrexate injection for other neoplastic diseases are investigational, and a therapeutic advantage has not been established.

Pregnancy:

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. Some products are contraindicated in pregnant women.

Bone marrow suppression:

Unexpectedly severe (sometimes fatal) bone marrow suppression, aplastic anemia, and toxicity have been reported with concomitant administration of methotrexate (usually in high dosage) along with some nonsteroidal anti-inflammatory drugs (NSAIDs).

Renal impairment:

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.

Hepatotoxicity:

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.

Pneumonitis:

Methotrexate-induced lung disease, including acute or chronic interstitial pneumonitis, is a potentially dangerous lesion, which may occur acutely at any time during therapy and has been reported at low doses. It is not always fully reversible and fatalities have been reported. Pulmonary symptoms (especially a dry, nonproductive cough) may require interruption of treatment and careful investigation.

Gastrointestinal toxicity:

Unexpectedly severe (sometimes fatal) gastrointestinal toxicity has been reported with concomitant administration of methotrexate (usually in high dosage) along with some nonsteroidal anti-inflammatory drugs (NSAIDs). Diarrhea and ulcerative stomatitis require interruption of therapy; otherwise hemorrhagic enteritis and death from intestinal perforation may occur.

Secondary malignancy:

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.

Tumor lysis syndrome:

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.

Dermatologic toxicity:

Severe, occasionally fatal skin reactions have been reported following single or multiple doses of methotrexate. Reactions have occurred within days of oral, intramuscular, intravenous, or intrathecal methotrexate administration. Recovery has been reported with discontinuation of therapy.

Opportunistic infections:

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

Radiotherapy:

Methotrexate given concomitantly with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis.

Experienced physician (injection):

Methotrexate should be used only by health care providers whose knowledge and experience include the use of antimetabolite therapy.

Brand Names: US

Otrexup; Rasuvo; Rheumatrex [DSC]; Trexall; Xatmep

Brand Names: Canada

Apo-Methotrexate; JAMP-Methotrexate; Methotrexate Injection USP; Methotrexate Injection, BP; Methotrexate Sodium Injection; Metoject; ratio-Methotrexate Sodium

Pharmacologic Category

Antineoplastic Agent, Antimetabolite (Antifolate); Antirheumatic, Disease Modifying; Immunosuppressant Agent

Dosing: Adult

Note: Methotrexate doses between 100 to 500 mg/m^2 **may require** leucovorin calcium rescue. Doses >500 mg/m^2 **require** leucovorin calcium rescue (refer to Dosing – Adjustment for Toxicity for leucovorin calcium dosing). Doses ≥250 mg/m^2 (IV) are associated with moderate emetic potential. Antiemetics may be recommended to prevent nausea and vomiting.

Acute lymphoblastic leukemia (ALL):

Meningeal leukemia prophylaxis or treatment: Intrathecal: Manufacturer's labeling: 12 mg (maximum 15 mg/dose) every 2 to 7 days; continue for 1 dose beyond CSF cell count normalization. **Note:** Optimal intrathecal chemotherapy dosing should be based on age rather than on body surface area (BSA); CSF volume correlates with age and not to BSA (Bleyer 1983; Kerr 2001).

CALGB 8811 regimen (Larson, 1995; combination therapy):

Early intensification: Intrathecal: 15 mg day 1 of early intensification phase, repeat in 4 weeks

CNS prophylaxis/interim maintenance phase:

Intrathecal: 15 mg day 1, 8, 15, 22, and 29

Oral: 20 mg/m^2 days 36, 43, 50, 57, and 64

Prolonged maintenance: Oral: 20 mg/m^2 days 1, 8, 15, and 22 every 4 weeks for 24 months from diagnosis

Dose-intensive regimen (Kantarjian, 2000; combination therapy):

IV: 200 mg/m^2 over 2 hours, followed by 800 mg/m^2 over 24 hours beginning day 1, (followed by leucovorin rescue) of even numbered cycles (in combination with cytarabine; alternates with Hyper-CVAD)

CNS prophylaxis: Intrathecal: 12 mg on day 2 of each cycle; duration depends on risk

Maintenance: IV: 10 mg/m^2/day for 5 days every month for 2 years (in combination with prednisone, vincristine, and mercaptopurine)

Breast cancer: IV: CMF regimen: 40 mg/m^2 days 1 and 8 every 4 weeks (in combination with cyclophosphamide and fluorouracil) for 6 to 12 cycles (Bonadonna 1995; Levine 1998)

Choriocarcinoma, chorioadenoma, gestational trophoblastic diseases: 15 to 30 mg oral or IM daily for a 5 day course; may repeat for 3 to 5 courses (manufacturer's labeling) **or** 100 mg/m^2 IV over 30 minutes followed by 200 mg/m^2 IV over 12 hours (with leucovorin 24 hours after the start of methotrexate), administer a second course if hCG levels plateau for 3 consecutive weeks (Garrett 2002) **or** 100 mg/m^2 IV push followed by 200 mg/m^2 IV over 12 hours on day 1 (with leucovorin 24 hours after the start of methotrexate; in combination with dactinomycin, etoposide, vincristine, and cyclophosphamide) every 14 days and continuing for at least 2 cycles after hCG level is normal (Escobar 2003; Lurain 2006)

Head and neck cancer, advanced: IV: 40 mg/m^2 once weekly until disease progression or unacceptable toxicity (Forastiere 1992; Guardiola 2004; Stewart 2009)

Lymphoma, non-Hodgkin: IV:

CODOX-M/IVAC regimen (Mead, 2008): Cycles 1 and 3 of CODOX-M (CODOX-M alternates with IVAC)

Adults ≤65 years: IV: 300 mg/m^2 over 1 hour (on day 10) followed by 2700 mg/m^2 over 23 hours (with leucovorin rescue)

Adults >65 years: IV: 100 mg/m^2 over 1 hour (on day 10) followed by 900 mg/m^2 over 23 hours (with leucovorin rescue)

Hyper-CVAD alternating with high-dose methotrexate/cytarabine regimen: IV: 1000 mg/m^2 over 24 hours on day 1 during even courses (2, 4, 6, and 8) of 21-day treatment cycles (Thomas 2006) **or** 200 mg/m^2 bolus day 1 followed by 800 mg/m^2 over 24 hours during even courses (2, 4, 6, and 8) of 21-day treatment cycles (Khouri 1998) with leucovorin rescue

Mycosis fungoides (cutaneous T-cell lymphoma): 5 to 50 mg once weekly or 15 to 37.5 mg twice weekly orally or IM for early stages (manufacturer's labeling) **or** 25 mg orally once weekly, may increase to 50 mg once weekly (Zackheim 2003)

Osteosarcoma: Adults ≤30 years: IV: MAP regimen: 12 g/m^2 (maximum: 20 g/dose) over 4 hours (followed by leucovorin rescue) for 4 doses during induction (before surgery) at weeks 4, 5, 9, and 10, and for 8 doses during maintenance (after surgery) at weeks 15, 16, 20, 21, 24, 25, 28, and 29 (in combination with doxorubicin and cisplatin) (Bielack 2015; Whelan 2015); other combinations, intervals, age ranges, and doses (8 to 14 g/m^2/dose) have been described (with leucovorin rescue), refer to specific reference for details (Bacci 2000; Bacci 2003; Goorin 2003; Le Deley 2007; Meyers 1992; Meyers 2005; Weiner 1986; Winkler 1988)

Psoriasis: Note: Some experts recommend concomitant folic acid 1 to 5 mg daily (except the day of methotrexate) to reduce hematologic, gastrointestinal, and hepatic adverse events related to methotrexate.

Oral: Initial: 2.5 to 5 mg/dose every 12 hours for 3 doses per week **or**

Oral, IM, IV, SubQ: Initial: 10 to 25 mg given once weekly; adjust dose gradually to optimal response (doses above 20 mg once weekly are associated with an increased incidence of toxicity); doses >30 mg per week should not be exceeded.

Note: An initial test dose of 2.5 to 5 mg is recommended in patients with risk factors for hematologic toxicity or renal impairment. (Kalb, 2009).

Rheumatoid arthritis: Note: Some experts recommend concomitant folic acid at a dose of least 5 mg per week (except the day of methotrexate) to reduce hematologic, gastrointestinal, and hepatic adverse events related to methotrexate.

Oral (manufacturer labeling): Initial: 7.5 mg once weekly or 2.5 mg every 12 hours for 3 doses per week; adjust dose gradually to optimal response (dosage exceeding 20 mg once weekly are associated with an increased incidence of toxicity; *alternatively*, 10 to 15 mg once weekly, increased by 5 mg every 2 to 4 weeks to a maximum of 20 to 30 mg once weekly has been recommended by some experts. Consider parenteral therapy with inadequate response or intolerance to oral therapy (Visser 2009).

SubQ: Initial: 7.5 mg once weekly; adjust dose gradually to optimal response (doses above 20 mg once weekly are associated with an increased incidence of toxicity)

IM: 7.5 mg once weekly; adjust dose gradually to optimal response (doses above 20 mg once weekly are associated with an increased incidence of toxicity)

Off-label uses:

Acute promyelocytic leukemia (APL) maintenance phase:

Oral: 15 mg/m^2 once weekly for 2 years (Ades 2008) or 20 mg/m^2 once weekly for 1 year (Powell 2010)

IM: 15 mg/m^2 once weekly for 2 years (Sanz 2004)

Bladder cancer (off-label use): IV:

Dose-dense MVAC regimen: 30 mg/m^2 day 1 every 2 weeks (in combination with vinblastine, doxorubicin, and cisplatin) (Sternberg 2001)

CMV regimen: 30 mg/m^2 days 1 and 8 every 3 weeks for 3 cycles (in combination with cisplatin, vinblastine and leucovorin rescue) (Griffiths 2011)

CNS lymphoma (off-label use): IV: 8000 mg/m^2 over 4 hours (followed by leucovorin rescue) every 14 days until complete response or a maximum of 8 cycles; if complete response, follow with 2 consolidation cycles at the same dose every 14 days (with leucovorin rescue), followed by 11 maintenance cycles of 8000 mg/m^2 every 28 days with leucovorin rescue (Batchelor 2003) **or** 2500 mg/m^2 over 2 to 3 hours every 14 days for 5 doses (in combination with vincristine, procarbazine, intrathecal methotrexate, leucovorin, dexamethasone, and cytarabine) (De Angelis 2002) **or** 3500 mg/m^2 over 2 hours on day 2 every 2 weeks (in combination with rituximab, vincristine, procarbazine, and leucovorin [with intra-omaya methotrexate 12 mg between days 5 and 12 of each cycle if positive CSF cytology]) for 5 to 7 induction cycles (Shah 2007)

Crohn disease, moderate/severe, corticosteroid-dependent or refractory (off-label use):

Remission induction or reduction of steroid use: IM, SubQ: 25 mg once weekly (Lichtenstein 2009)

Remission maintenance: IM: 15 mg once weekly (Feagan 2000; Lichtenstein 2009)

Dermatomyositis/polymyositis (off-label uses):

Oral: Initial: 7.5 to 15 mg per week, often adjunctively with high-dose corticosteroid therapy; may increase in weekly 2.5 mg increments to target dose of 10 to 25 mg per week (**Note:** Administration of folate 5 to 7 mg per week has been used to reduce side effects) (Briemberg 2003; Newman 1995; Wiendl 2008).

IV, IM: Doses of 20 to 60 mg/week have been employed if failure with oral therapy (doses >50 mg/week may require leucovorin calcium rescue) (Briemberg 2003)

Ectopic pregnancy (off-label use): IM:

Single-dose regimen: Methotrexate 50 mg/m^2 on day 1; Measure serum hCG levels on days 4 and 7; if needed, repeat dose on day 7 (ACOG 2008; ASRM 2006; Barnhart 2009)

Two-dose regimen: Methotrexate 50 mg/m^2 on day 1; Measure serum hCG levels on day 4 and administer a second dose of methotrexate 50 mg/m^2; Measure serum hCG levels on day 7 and if needed, administer a third dose of 50 mg/m^2 (ACOG 2008; Barnhart 2009)

Multidose regimen: Methotrexate 1 mg/kg on day 1; leucovorin calcium 0.1 mg/kg IM on day 2; measure serum hCG on day 2; methotrexate 1 mg/kg on day 3; leucovorin calcium 0.1 mg/kg on day 4; measure serum hCG on day 4; continue up to a total of 4 courses based on hCG concentrations (ACOG 2008; ASRM 2006; Barnhart 2009)

Graft-versus-host disease, acute (aGVHD), prophylaxis: IV: 15 mg/m^2/dose on day 1 and 10 mg/m^2/dose on days 3 and 6 after allogeneic transplant (in combination with cyclosporine and prednisone) (Chao 1993; Chao 2000; Ross 1999) **or** 15 mg/m^2/dose on day 1 and 10 mg/m^2/dose on days 3, 6, and 11 after allogeneic transplant (in combination with cyclosporine) (Chao 2000) **or** 15 mg/m^2/dose on day 1 and 10 mg/m^2/dose on days 3, 6, and 11 after allogeneic transplant (in

combination with cyclosporine, followed by leucovorin); may omit day 11 methotrexate for grade 2 or higher toxicity (Ruutu 2013)

Multiple sclerosis (off-label use): Oral: 7.5 or 20 mg once weekly either alone or as add-on therapy to interferon beta-1a (Calabresi 2002; Goodkin 1996; Lugaresi 2001)

Nonleukemic meningeal cancer (off-label uses): Intrathecal: 12 mg/dose twice weekly for 4 weeks, then weekly for 4 doses, then monthly for 4 doses (Glantz 1998) **or** 10 mg twice weekly for 4 weeks, then weekly for 1 month, then every 2 weeks for 2 months (Glantz 1999) **or** 10 to 15 mg twice weekly for 4 weeks, then once weekly for 4 weeks, then a maintenance regimen of once a month (Chamberlain, 2010)

Soft tissue sarcoma (desmoid tumors, aggressive fibromatosis), advanced (off-label use): IV: 30 mg/m^2 every 7 to 10 days (dose usually rounded to 50 mg) in combination with vinblastine for 1 year (Azzarelli, 2001)

Systemic lupus erythematosus, moderate-to-severe (off-label use): Oral: Initial: 7.5 mg once weekly; may increase by 2.5 mg increments weekly (maximum: 20 mg once weekly), in combination with prednisone (Fortin, 2008)

Takayasu arteritis, refractory or relapsing disease (off-label use): Oral: Initial dose: 0.3 mg/kg/week (maximum: 15 mg per week), titrated by 2.5 mg increments every 1 to 2 weeks until reaching a maximum tolerated weekly dose of 25 mg (use in combination with a corticosteroid; Hoffman 1994)

Uveitis (off-label use): Oral: 7.5 to 20 mg once weekly either alone or in conjunction with other corticosteroids/immunosuppressants (Diaz-Llopis 2009; Galor 2008; Kaplan-Messas 2003; Munoz-Fernandez 2009)

Dosing: Pediatric

(For additional information see "Methotrexate: Pediatric drug information")

Note: Methotrexate doses between 100 to 500 mg/m^2 **may require** leucovorin calcium rescue. Doses >500 mg/m^2 **require** leucovorin calcium rescue (refer to Dosing – Adjustment for Toxicity for leucovorin calcium dosing). In children, doses ≥12 g/m^2 (IV) are associated with a high emetic potential; doses ≥250 mg/m^2 (IV) are associated with moderate emetic potential (Dupuis 2011). Antiemetics may be recommended to prevent nausea and vomiting.

Polyarticular juvenile idiopathic arthritis (pJIA): Oral, IM, SubQ: Initial: 10 mg/m^2 once weekly, adjust gradually to optimum response; doses up to 20 to 30 mg/m^2 once weekly have been used (doses above 20 mg/m^2 once weekly may be associated with an increased risk of toxicity)

Acute lymphoblastic leukemia (ALL; intrathecal therapy is also administered [refer to specific reference]):

Consolidation/intensification phases (as part of a combination regimen): 1,000 mg/m^2 IV over 24 hours in week 1 of intensification and 20 mg/m^2 IM (use 50% dose reduction if on same day as intrathecal methotrexate) on day 1 of week 2 of intensification phase; Intensification repeats every 2 weeks for a total of 12 courses (Mahoney 2000) **or** 5000 mg/m^2 IV over 24 hours days 8, 22, 36, and 50 of consolidation phase (Schrappe 2000) with leucovorin rescue

Interim maintenance (as part of a combination regimen): 15 mg/m^2 orally days 0, 7, 14, 21, 28, and 35 of interim maintenance phase (Seibel 2008) **or** 100 mg/m^2 (escalate dose by 50 mg/m^2 each dose) IV days 0, 10, 20, 30, and 40 of increased intensity interim maintenance phase (Seibel 2008)

Maintenance (as part of a combination regimen): 20 mg/m^2 IM weekly on day 1 of weeks 25 to 130 (Mahoney 2000) **or** 20 mg/m^2 orally days 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, and 77 (Seibel, 2008)

T-cell acute lymphoblastic leukemia (Asselin 2011; triple intrathecal therapy is also administered [refer to specific reference]):

Induction (weeks 1 to 6; as part of a combination regimen): IV:

Low dose: 40 mg/m^2 day 2

High dose: 500 mg/m^2 over 30 minutes followed by 4500 mg/m^2 over 23.5 hours (with leucovorin rescue) day 22

Consolidation (weeks 7 to 33; combination chemotherapy): IV: High dose: 500 mg/m^2 over 30 minutes followed by 4500 mg/m^2 over 23.5 hours (with leucovorin rescue) in weeks 7, 10, and 13 with leucovorin rescue

Continuation (weeks 34 to 108; combination chemotherapy): IV, IM: 30 mg/m^2 weekly until 2 years after documented complete remission

ALL, CNS prophylaxis triple intrathecal therapy (off-label dosing): Intrathecal: Age-based dosing (in combination with cytarabine and hydrocortisone): Days of administration vary based on risk status and protocol; refer to institutional protocols or reference for details (Matloub 2006):

<2 years: 8 mg

2 to <3 years: 10 mg

3 to ≤8 years: 12 mg

>8 years: 15 mg

Meningeal leukemia, prophylaxis or treatment: Intrathecal: 6 to 12 mg/dose (based on age) every 2 to 7 days; continue for 1 dose beyond CSF cell count normalization. **Note:** Optimal intrathecal chemotherapy dosing should be based on age rather than on body surface area (BSA); CSF volume correlates with age and not to BSA (Bleyer 1983; Kerr 2001):

<1 year: 6 mg/dose

1 year: 8 mg/dose

2 years: 10 mg/dose

≥3 years: 12 mg/dose

Osteosarcoma: IV: MAP regimen: 12 g/m^2 (maximum: 20 g/dose) over 4 hours (followed by leucovorin rescue) for 4 doses during induction (before surgery) at weeks 4, 5, 9, and 10, and for 8 doses during maintenance (after surgery) at weeks 15, 16, 20, 21, 24, 25, 28, and 29 (in combination with doxorubicin and cisplatin) (Bielack 2015; Whelan 2015); other combinations, intervals, and doses (8 to 14 g/m^2/dose) have been described (with leucovorin rescue), refer to specific reference for details (Bacci 2000; Bacci 2003; Goorin 2003; Le Deley 2007; Meyers 1992; Meyers 2005; Weiner 1986; Winkler 1988)

Crohn disease, induction and maintenance (off-label use): SubQ: 15 mg/m^2 once weekly; maximum dose: 25 mg (Rufo 2012)

Dermatomyositis (off-label use): Oral, SubQ (preferred): The lesser of 15 mg/m^2 or 1 mg/kg once weekly (maximum dose: 40 mg/week) in combination with corticosteroids (Huber 2010) **or** 15 mg/m^2 once weekly (range: 10 to 20 mg/m^2 once weekly; maximum dose: 25 mg/week) in combination with prednisone (Ramanan 2005)

Graft-versus-host disease, acute (aGVHD) prophylaxis (off-label use): IV: Refer to adult dosing.

Dosing: Geriatric

Refer to adult dosing; adjust for renal impairment.

Breast cancer: Patients >60 years: IV: CMF regimen: 30 mg/m^2 days 1 and 8 every 4 weeks (in combination with cyclophosphamide and fluorouracil) for up to 12 cycles (Bonadonna, 1995)

Meningeal leukemia: Intrathecal: Consider a dose reduction (CSF volume and turnover may decrease with age)

Non-Hodgkin lymphoma: CODOX-M/IVAC regimen (Mead, 2008): Cycles 1 and 3 of CODOX-M (CODOX-M alternates with IVAC): IV: 100 mg over 1 hour (on day 10) followed by 900 mg over 23 hours (with leucovorin rescue)

Rheumatoid arthritis/psoriasis: Oral: Initial: 5 to 7.5 mg per week, not to exceed 20 mg per week

Dosing: Renal Impairment

There are no dosage adjustments provided in the manufacturer's labeling. The following adjustments have been recommended:

Aronoff, 2007:

Adults:

CrCl 10 to 50 mL/minute: Administer 50% of dose

CrCl <10 mL/minute: Avoid use

Intermittent hemodialysis: Administer 50% of dose (post dialysis)

Continuous renal replacement therapy (CRRT): Administer 50% of dose

Children:

CrCl 10 to 50 mL/minute/1.73 m^2: Administer 50% of dose

CrCl <10 mL/minute/1.73 m^2: Administer 30% of dose

Intermittent hemodialysis: Administer 30% of dose (post dialysis)

Continuous ambulatory peritoneal dialysis (CAPD): Administer 30% of dose

Continuous renal replacement therapy (CRRT): Administer 50% of dose

Kintzel, 1995:

CrCl 46 to 60 mL/minute: Administer 65% of normal dose

CrCl 31 to 45 mL/minute: Administer 50% of normal dose

CrCl <30 mL/minute: Avoid use

Hemodialysis patients with cancer (Janus, 2010): Administer 25% of dose after hemodialysis; monitor closely for toxicity

High-dose methotrexate, dose-intensive regimen for ALL (200 mg/m^2 over 2 hours, followed by 800 mg/m^2 over 24 hours with leucovorin rescue [Kantarjian, 2000]):

Serum creatinine <1.5 mg/dL: No dosage adjustment necessary

Serum creatinine 1.5 to 2 mg/dL: Administer 75% of dose

Serum creatinine >2 mg/dL: Administer 50% of dose

Dosing: Hepatic Impairment There are no dosage adjustments provided in the manufacturer's labeling; use with caution in patients with impaired hepatic function or preexisting hepatic damage. The following adjustments have been recommended (Floyd, 2006):

Bilirubin 3.1 to 5 mg/dL **or** transaminases >3 times ULN: Administer 75% of dose

Bilirubin >5 mg/dL: Avoid use

Dosing: Obesity *ASCO Guidelines for appropriate chemotherapy dosing in obese adults with cancer (excludes leukemias):* Utilize patient's actual body weight (full weight) for calculation of body surface area- or weight-based dosing, particularly when the intent of therapy is curative; manage regimen-related toxicities in the same manner as for nonobese patients; if a dose reduction is utilized due to toxicity, consider resumption of full weight-based dosing with subsequent cycles, especially if cause of toxicity (eg, hepatic or renal impairment) is resolved (Griggs, 2012).

Dosing: Adjustment for Toxicity

Methotrexate toxicities:

Nonhematologic toxicity: Diarrhea, stomatitis, or vomiting which may lead to dehydration: Discontinue until recovery

Hematologic toxicity:

Psoriasis, rheumatoid arthritis: Significant blood count decrease: Discontinue immediately.

Oncologic uses: Profound granulocytopenia and fever: Evaluate immediately; consider broad-spectrum parenteral antimicrobial coverage

Leucovorin calcium dosing (from methotrexate injection prescribing information; other leucovorin dosing/schedules may be specific to chemotherapy protocols):

Normal methotrexate elimination (serum methotrexate level ~10 micromolar at 24 hours after administration, 1 micromolar at 48 hours, and <0.2 micromolar at 72 hours): Leucovorin calcium 15 mg (oral, IM, or IV) every 6 hours for 60 hours (10 doses) beginning 24 hours after the start of methotrexate infusion

Delayed late methotrexate elimination (serum methotrexate level remaining >0.2 micromolar at 72

hours and >0.05 micromolar at 96 hours after administration): Continue leucovorin calcium 15 mg (oral, IM or IV) every 6 hours until methotrexate level is <0.05 micromolar

Delayed early methotrexate elimination and/or acute renal injury (serum methotrexate level ≥50 micromolar at 24 hours, or ≥5 micromolar at 48 hours, or a doubling of serum creatinine level at 24 hours after methotrexate administration): Leucovorin calcium 150 mg IV every 3 hours until methotrexate level is <1 micromolar, then 15 mg IV every 3 hours until methotrexate level <0.05 micromolar

Leucovorin nomogram dosing for high-dose methotrexate overexposure (**generalized dosing** derived from reference nomogram figures, refer to each reference [Bleyer, 1978; Bleyer, 1981; Widemann, 2006] or institution-specific nomogram for details):

At 24 hours:

For methotrexate levels of ≥100 micromolar at ~24 hours, leucovorin is initially dosed at 1000 mg/m^2 every 6 hours

For methotrexate levels of ≥10 to <100 micromolar at 24 hours, leucovorin is initially dosed at 100 mg/m^2 every 3 or 6 hours

For methotrexate levels of ~1 to 10 micromolar at 24 hours, leucovorin is initially dosed at 10 mg/m^2 every 3 or 6 hours

At 48 hours:

For methotrexate levels of ≥100 micromolar at 48 hours, leucovorin is dosed at 1000 mg/m^2 every 6 hours

For methotrexate levels of ≥10 to <100 micromolar at 48 hours, leucovorin is dosed at 100 mg/m^2 every 3 hours

For methotrexate levels of ~1 to 10 micromolar at 48 hours, leucovorin is dosed at 100 mg/m^2 every 6 hours **or** 10 to 100 mg/m^2 every 3 hours

At 72 hours:

For methotrexate levels of ≥10 micromolar at 72 hours, leucovorin is dosed at 100 to 1000 mg/m^2 every 3 to 6 hours

For methotrexate levels of ~1 to 10 micromolar at 72 hours, leucovorin is dosed at 10 to 100 mg/m^2 every 3 hours

For methotrexate levels of ~0.1 to 1 micromolar at 72 hours, leucovorin is dosed at 10 mg/m^2 every 3 to 6 hours

If serum creatinine is increased more than 50% above baseline, increase the standard leucovorin dose to 100 mg/m^2 every 3 hours, then adjust according to methotrexate levels above.

Follow methotrexate levels daily, leucovorin may be discontinued when methotrexate level is <0.1 micromolar

Dosage Forms

Excipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Solution, Injection:

Generic: 250 mg/10 mL (10 mL); 50 mg/2 mL (2 mL)

Solution, Injection [preservative free]:

Generic: 1 g/40 mL (40 mL); 100 mg/4 mL (4 mL); 200 mg/8 mL (8 mL); 250 mg/10 mL (10 mL); 50 mg/2 mL (2 mL)

Solution, Oral:

Xatmep: 2.5 mg/mL (120 mL) [contains methylparaben sodium, propylparaben sodium]

Solution Auto-injector, Subcutaneous [preservative free]:

Otrexup: 7.5 mg/0.4 mL (0.4 mL); 10 mg/0.4 mL (0.4 mL); 12.5 mg/0.4 mL (0.4 mL); 15 mg/0.4 mL (0.4 mL); 17.5 mg/0.4 mL (0.4 mL); 20 mg/0.4 mL (0.4 mL); 22.5 mg/0.4 mL (0.4 mL); 25 mg/0.4mL (0.4 mL)

Rasuvo: 7.5 mg/0.15 mL (0.15 mL); 10 mg/0.2 mL (0.2 mL); 12.5 mg/0.25 mL (0.25 mL); 15 mg/0.3 mL (0.3 mL); 17.5 mg/0.35 mL (0.35 mL); 20 mg/0.4 mL (0.4 mL); 22.5 mg/0.45 mL (0.45 mL); 25 mg/0.5 mL (0.5 mL); 27.5 mg/0.55 mL (0.55 mL); 30 mg/0.6 mL (0.6 mL)

Solution Reconstituted, Injection [preservative free]:

Generic: 1 g (1 ea)

Tablet, Oral:

Rheumatrex: 2.5 mg [DSC] [scored]

Trexall: 5 mg, 7.5 mg, 10 mg, 15 mg [scored]

Generic: 2.5 mg

Generic Equivalent Available (US) May be product dependent

Product Availability Xatmep (methotrexate 2.5 mg/mL oral solution): FDA approved April 2017; availability anticipated in June 2017. Information pertaining to this product within the monograph is pending revision. Consult the prescribing information for additional information.

Administration

In children, doses ≥12 g/m^2 are associated with a high emetic potential; doses ≥250 mg/m^2 (IV) in adults and children are associated with moderate emetic potential (Dupuis, 2011). Antiemetics may be recommended to prevent nausea and vomiting.

Methotrexate may be administered orally, IM, IV, intrathecally, or SubQ; IV administration may be as slow push (10 mg/minute), bolus infusion, or 24-hour continuous infusion (route and rate of administration depend on indication and/or protocol; refer to specific references). Must use preservative-free formulation for intrathecal or high-dose methotrexate administration.

Specific dosing schemes vary, but high doses should be followed by leucovorin calcium rescue to prevent

toxicity.

Otrexup and Rasuvo are autoinjectors for once weekly subcutaneous use in the abdomen or thigh; patient may self-administer after appropriate training. 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.

Hazardous Drugs Handling Considerations

Hazardous agent (NIOSH 2016 [group 1]).

Use appropriate precautions for receiving, handling, administration, and disposal. Gloves (single) should be worn during receiving, unpacking, and placing in storage. NIOSH recommends single gloving for administration of intact tablets or capsules. For injection preparation, NIOSH recommends double gloving, a protective gown, ventilated engineering controls (a class II biological safety cabinet or a compounding aseptic containment isolator), and closed system transfer devices (CSTDs). Double gloving, a gown, and (if dosage form allows) CSTDs are required during injection administration (NIOSH 2016).

Use

Oncology uses: Acute lymphoblastic leukemia (ALL) maintenance treatment, ALL meningeal leukemia (preservative-free only; prophylaxis and treatment); treatment of trophoblastic neoplasms (gestational choriocarcinoma, chorioadenoma destruens and hydatidiform mole), breast cancer, head and neck cancer (epidermoid), cutaneous T-Cell lymphoma (advanced mycosis fungoides), lung cancer (squamous cell and small cell), advanced non-Hodgkin lymphomas (NHL), osteosarcoma (preservative-free only).

Nononcology uses: Treatment of psoriasis (severe, recalcitrant, disabling) that is unresponsive to other therapies; severe, active rheumatoid arthritis (RA) that is unresponsive to or intolerant of first-line therapy including full dose nonsteroidal anti-inflammatory agents (NSAIDs); active polyarticular-course juvenile idiopathic arthritis (pJIA) that is unresponsive to or intolerant of first-line therapy including full dose nonsteroidal anti-inflammatory agents (NSAIDs).

Limitations of use: Otrexup and Rasuvo are not indicated for the treatment of neoplastic diseases.

Guideline recommendations: Rheumatoid arthritis: Treatment initiation with a disease-modifying antirheumatic drug (DMARD) is recommended in DMARD-naïve patients with either early rheumatoid arthritis (RA) (disease duration <6 months) or established RA (disease duration ≥6 months). Methotrexate is the preferred initial DMARD for most early or established RA patients (Singh [ACR 2016]).

Use: Off-Label

Abortion (medical management); Acute graft-versus-host disease (prophylaxis); Acute promyelocytic leukemia (APL) maintenance (adults); Bladder cancer; CNS lymphoma; Crohn disease (maintenance of remission); Dermatomyositis/polymyositis; Ectopic pregnancy; Multiple sclerosis; Nonleukemic meningeal cancer; Soft tissue sarcoma (desmoid tumors, aggressive fibromatosis), advanced; Systemic lupus erythematosus, moderate-to-severe; Takayasu arteritis, refractory or relapsing disease; Uveitis (adults)

Medication Safety Issues

Sound-alike/look-alike issues:

Methotrexate may be confused with mercaptopurine, methylPREDNISolone sodium succinate, metOLazone, metroNIDAZOLE, mitoXANTRONE, PRALAtrexate

High alert medication:

The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Administration issues:

Errors have occurred (resulting in death) when methotrexate was administered as “daily” dose instead of “weekly” dose recommended for some indications. The ISMP recommends hospitals use a weekly dosage regimen default for oral methotrexate orders, with a hard stop override requiring verification of appropriate oncology indication; manual systems should require verification of an oncology indication prior to dispensing oral methotrexate for daily administration. Pharmacists should provide patient education for patients discharged on weekly oral methotrexate (ISMP, 2014).

Intrathecal medication safety: The American Society of Clinical Oncology (ASCO)/Oncology Nursing Society (ONS) chemotherapy administration safety standards (Jacobson, 2009) encourage the following safety measures for intrathecal chemotherapy:

- Intrathecal medication should not be prepared during the preparation of any other agents
- After preparation, keep in an isolated location or container clearly marked with a label identifying as "intrathecal" use only
- Delivery to the patient should only be with other medications also intended for administration into the central nervous system

Other safety concerns:

MTX is an error-prone abbreviation (mistaken as mitoxantrone or multivitamin)

International issues:

Trexall [US] may be confused with Trexol brand name for tramadol [Mexico]; Truxal brand name for chlorprothixene [multiple international markets]

Adverse Reactions

Note: Adverse reactions vary by route and dosage. Frequency not always defined.

Cardiovascular: Arterial thrombosis, cerebral thrombosis, chest pain, deep vein thrombosis, hypotension, pericardial effusion, pericarditis, plaque erosion (psoriasis), pulmonary embolism, retinal thrombosis, thrombophlebitis, vasculitis

Central nervous system: Dizziness (≤3%), headache (pJIA 1%), abnormal cranial sensation, brain disease, chemical arachnoiditis (intrathecal; acute), chills, cognitive dysfunction (has been reported at low dosage), drowsiness, fatigue, leukoencephalopathy (intravenous administration after craniospinal irradiation or repeated high-dose therapy; may be chronic), malaise, mood changes (has been reported at low dosage), neurological signs and symptoms (at high dosages; including confusion, hemiparesis, transient blindness, seizures, and coma), severe neurotoxicity (reported with unexpectedly increased frequency among pediatric patients with acute lymphoblastic leukemia who were treated with intermediate-dose intravenous methotrexate), speech disturbance

Dermatologic: Alopecia (≤10%), burning sensation of skin (psoriasis 3% to 10%), skin photosensitivity (3% to 10%), skin rash (≤3%), dermatitis (rheumatoid arthritis 1% to 3%), pruritus (rheumatoid arthritis 1% to 3%), acne vulgaris, dermal ulcer, diaphoresis, ecchymoses, erythema multiforme, erythematous rash, exfoliative dermatitis, furunculosis, hyperpigmentation, hypopigmentation, skin abnormalities related to radiation recall, skin necrosis, Stevens-Johnson syndrome, telangiectasia, toxic epidermal necrolysis, urticaria

Endocrine & metabolic: Decreased libido, decreased serum albumin, diabetes mellitus, gynecomastia, menstrual disease

Gastrointestinal: Diarrhea (≤11%), nausea and vomiting (≤11%), stomatitis (2% to 10%), abdominal distress, anorexia, aphthous stomatitis, enteritis, gastrointestinal hemorrhage, gingivitis, hematemesis, intestinal perforation, melena

Genitourinary: Azotemia, cystitis, defective oogenesis, defective spermatogenesis, dysuria, hematuria, impotence, infertility, oligospermia, pancreatitis, proteinuria, severe renal disease, vaginal discharge

Hematologic & oncologic: Thrombocytopenia (rheumatoid arthritis 3% to 10%; platelet count $<100,000/mm^3$), leukopenia (1% to 3%; WBC $<3000/mm^3$), pancytopenia (rheumatoid arthritis 1% to 3%), agranulocytosis, anemia, aplastic anemia, bone marrow depression (nadir: 7-10 days), decreased hematocrit, eosinophilia, gastric ulcer, hypogammaglobulinemia, lymphadenopathy, lymphoma, lymphoproliferative disorder, neutropenia, non-Hodgkin's lymphoma (in patients receiving low-dose oral methotrexate), tumor lysis syndrome

Hepatic: Increased liver enzymes (14% to 15%), cirrhosis (chronic therapy), hepatic failure, hepatic fibrosis (chronic therapy), hepatitis (acute), hepatotoxicity

Hypersensitivity: Anaphylactoid reaction

Infection: Cryptococcosis, cytomegalovirus disease (including cytomegaloviral pneumonia, sepsis, nocardiosis), herpes simplex infection, herpes zoster, histoplasmosis, infection, vaccinia (disseminated; following smallpox immunization)

Neuromuscular & skeletal: Arthralgia, myalgia, myelopathy (subacute), osteonecrosis (with radiotherapy), osteoporosis, stress fracture

Ophthalmic: Blurred vision, conjunctivitis, eye pain, visual disturbance

Otic: Tinnitus

Renal: Renal failure

Respiratory: Interstitial pneumonitis (rheumatoid arthritis 1%), chronic obstructive pulmonary disease, cough, epistaxis, pharyngitis, pneumonia (including *Pneumocystis jiroveci*), pulmonary alveolitis,

pulmonary disease, pulmonary fibrosis, respiratory failure, upper respiratory tract infection

Miscellaneous: Fever, nodule, tissue necrosis

Contraindications

Known hypersensitivity to methotrexate or any component of the formulation; breast-feeding

Additional contraindications for patients with psoriasis or rheumatoid arthritis: Pregnancy, alcoholism, alcoholic liver disease or other chronic liver disease, immunodeficiency syndromes (overt or laboratory evidence); preexisting blood dyscrasias (eg, bone marrow hypoplasia, leukopenia, thrombocytopenia, significant anemia)

Warnings/Precautions

Concerns related to adverse effects:

• Acute renal failure: May cause renal damage leading to acute renal failure, especially with high-dose methotrexate; monitor renal function and methotrexate levels closely, maintain adequate hydration and urinary alkalinization. Use with caution in osteosarcoma patients treated with high-dose methotrexate in combination with nephrotoxic chemotherapy (eg, cisplatin).

• Bone marrow suppression: **[US Boxed Warning]: Unexpectedly severe (sometimes fatal) bone marrow suppression and aplastic anemia have been reported with concomitant administration of methotrexate (usually in high dosage) along with some nonsteroidal anti-inflammatory drugs (NSAIDs);** anemia, pancytopenia, leukopenia, neutropenia, and/or thrombocytopenia may occur. Use with caution in patients with preexisting bone marrow suppression. Discontinue treatment (immediately) in rheumatoid arthritis (RA) or psoriasis if a significant decrease in hematologic components is noted.

• CNS effects: May cause neurotoxicity. Leukoencephalopathy has been reported (case reports), usually in patients who have received cranial irradiation and IV methotrexate. Chronic leukoencephalopathy has been reported with high-dose methotrexate (with leucovorin rescue and even without cranial irradiation) and with intrathecal methotrexate; discontinuing methotrexate does not always result in complete recovery; may be progressive and fatal. Serious neurotoxicity, including generalized and focal seizures has occurred (usually in pediatric ALL patients receiving intermediate-dose (1 g/m^2 IV methotrexate); leukoencephalopathy and/or microangiopathic calcifications were noted on diagnostic imaging studies in symptomatic patients. A transient acute stroke-like encephalopathy has been observed, usually with high-dose regimens; manifestations may include confusion, hemiparesis, transient blindness, seizure, and coma. Chemical arachnoiditis (headache, back pain, nuchal rigidity, fever) and myelopathy may result from intrathecal administration. May cause dizziness and fatigue; may affect the ability to drive or operate heavy machinery.

• Dermatologic toxicity: **Severe, occasionally fatal skin reactions have been reported following single or multiple doses of methotrexate. Reactions have occurred within days of oral, intramuscular, intravenous, or intrathecal methotrexate administration. Recovery has been reported with discontinuation of therapy.** Dermatologic reactions have included toxic epidermal necrolysis, Stevens-Johnson syndrome, exfoliative dermatitis, skin necrosis, and erythema multiforme. Radiation dermatitis and sunburn may be precipitated by methotrexate administration.

Psoriatic lesions may be worsened by concomitant exposure to ultraviolet radiation.

• Fertility: May cause impairment of fertility, oligospermia, and menstrual dysfunction.

• Gastrointestinal toxicity: **[US Boxed Warning]: Gastrointestinal toxicity may occur (may be unexpectedly severe, usually occurs with high doses along with concomitant use of some NSAIDs); diarrhea and ulcerative stomatitis may require treatment interruption; otherwise hemorrhagic enteritis and death from intestinal perforation may occur.** Use with caution in patients with peptic ulcer disease, ulcerative colitis. In children, doses ≥12 g/m^2 (IV) are associated with a high emetic potential; doses ≥250 mg/m^2 (IV) in adults and children are associated with moderate emetic potential (Dupuis 2011). Antiemetics may be recommended to prevent nausea and vomiting.

• Hepatotoxicity: **[US Boxed Warning]: 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 often are not 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.** Risk is related to cumulative dose (≥1.5 g) and prolonged exposure. Monitor closely (with liver function tests, including serum albumin) for liver toxicities. Liver enzyme elevations may be noted, but may not be predictive of hepatic disease in long term treatment for psoriasis (but generally is predictive in RA treatment). Discontinue methotrexate with moderate to severe change in liver biopsy. Risk factors for hepatotoxicity include history of above moderate ethanol consumption, persistent abnormal liver chemistries, history of chronic liver disease (including hepatitis B or C), family history of inheritable liver disease, diabetes, obesity, hyperlipidemia, lack of folate supplementation during methotrexate therapy, cumulative methotrexate dose exceeding 1.5 g, continuous daily methotrexate dosing and history of significant exposure to hepatotoxic drugs. Use with caution with preexisting liver impairment; may require dosage reduction. Use with caution when used with other hepatotoxic agents (azathioprine, retinoids, sulfasalazine).

• Opportunistic infections: **[US Boxed Warning]: Immune suppression may lead to potentially fatal opportunistic infections, including *Pneumocystis jirovecii* pneumonia (PCP).** Use methotrexate with extreme caution in patients with an active infection (contraindicated in patients with immunodeficiency syndrome).

• Pneumonitis: **[US Boxed Warning]: Methotrexate-induced lung disease, including acute or chronic interstitial pneumonitis, is a potentially dangerous lesion, which may occur acutely at any time during therapy and has been reported at low doses. It is not always fully reversible and fatalities have been reported. Pulmonary symptoms (especially a dry, nonproductive cough) may require interruption of treatment and careful investigation.** Pulmonary symptoms may occur at any time during therapy and at any dosage; monitor closely for pulmonary symptoms, particularly dry, nonproductive cough. Other potential symptoms include fever, dyspnea, hypoxemia, or pulmonary infiltrate.

• Secondary malignancy: **[US Boxed Warning]: 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. Discontinue methotrexate if lymphoma does not regress. Other secondary tumors have been reported.

• Tumor lysis syndrome: **[US Boxed Warning]: Tumor lysis syndrome may occur in patients with high tumor burden; appropriate supportive and pharmacologic measures may prevent or alleviate tumor lysis syndrome.**

Disease-related concerns:

• Ascites/pleural effusions: **[US Boxed Warning]: Elimination is reduced in patients with ascites and/or pleural effusions;** resulting in prolonged half-life and toxicity; may require dose reduction or discontinuation. Monitor closely for toxicity.

• Hepatic impairment: Use with caution in patients with preexisting liver impairment.

• Peptic ulcer disease: Use with caution in patients with peptic ulcer disease; diarrhea and stomatitis may occur.

• Renal impairment: **[US Boxed Warning]: Methotrexate elimination is reduced in patients with renal impairment; monitor closely for toxicity; may require dose reduction or, in some cases, discontinuation of methotrexate administration.**

• Ulcerative colitis: Use with caution in patients with ulcerative colitis; diarrhea and stomatitis may occur.

Concurrent drug therapy issues:

• Drug-drug interactions: Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy. Consult drug interactions database for more detailed information.

• Hepatotoxic agents: Use caution when used with other hepatotoxic agents (azathioprine, retinoids, sulfasalazine).

• Mercaptopurine: Methotrexate may increase the levels and effects of mercaptopurine; may require dosage adjustments.

• Nephrotoxic chemotherapy: Use with caution in osteosarcoma patients treated with high-dose methotrexate in combination with nephrotoxic chemotherapy (eg, cisplatin).

• NSAIDs: Do not administer NSAIDs prior to or during high dose methotrexate therapy; may increase and prolong serum methotrexate levels. Doses used for psoriasis may still lead to unexpected toxicities; use with caution when administering NSAIDs or salicylates with lower doses of methotrexate for RA.

• Proton pump inhibitors: Concomitant use of proton pump inhibitors with methotrexate (primarily high-dose methotrexate) may elevate and prolong serum methotrexate levels and metabolite (hydroxymethotrexate) levels (based on case reports and pharmacokinetic studies). May lead to toxicities; use with caution.

• Vaccines: Immunization may be ineffective during methotrexate treatment. Immunization with live vaccines is not recommended; cases of disseminated vaccinia infections due to live vaccines have been reported.

• Vitamins: Vitamins containing folate may decrease response to systemic methotrexate; folate deficiency may increase methotrexate toxicity.

Special populations:

• Elderly: Use caution and monitor closely in the elderly; increased risk of toxicity.

• Pregnancy: **[US Boxed Warning]: Methotrexate has been reported to cause fetal death and/or congenital abnormalities. Methotrexate 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. Some products are contraindicated in pregnant women.**

• Radiotherapy recipients: **[US Boxed Warning]: Concomitant methotrexate administration with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis.**

Dosage form specific issues:

• Benzyl alcohol and derivatives: Some dosage forms may contain benzyl alcohol; large amounts of benzyl alcohol (≥99 mg/kg/day) have been associated with a potentially fatal toxicity ("gasping syndrome") in neonates; the "gasping syndrome" consists of metabolic acidosis, respiratory distress, gasping respirations, CNS dysfunction (including convulsions, intracranial hemorrhage), hypotension, and cardiovascular collapse (AAP ["Inactive" 1997]; CDC 1982); some data suggests that benzoate displaces bilirubin from protein binding sites (Ahlfors 2001); avoid or use dosage forms containing benzyl alcohol with caution in neonates. See manufacturer's labeling.

• Intrathecal and high-dose therapy: **[US Boxed Warnings]: Use only preservative-free methotrexate formulations and diluents for intrathecal and high-dose therapy. Do NOT use formulations or diluents containing preservatives for intrathecal and high-dose therapy because they contain benzyl alcohol.**

Other warnings/precautions:

• Administration schedules: Errors have occurred (some resulting in death) when methotrexate was administered as a "daily" dose instead of a "weekly" dose intended for some indications. The ISMP Targeted Medication Safety Best Practices for Hospitals recommends hospitals use a weekly dosage regimen default for oral methotrexate orders, with a hard stop override requiring verification of appropriate oncology indication; manual systems should require verification of an oncology indication prior to dispensing oral methotrexate for daily administration. Pharmacists should provide patient education for patients discharged on weekly oral methotrexate; education should include written leaflets that contain clear instructions about the weekly dosing schedule and explain the danger of taking extra doses (ISMP, 2014).

• Appropriate use: **[US Boxed Warnings]: 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, skin, and kidney toxicities. Patients should be informed by their physician of the risks involved and be under a physician's care throughout therapy. The use of methotrexate high-dose**

regimens recommended for osteosarcoma requires meticulous care. High-dose regimens of methotrexate injection for other neoplastic diseases are investigational, and a therapeutic advantage has not been established.

• Experienced physician: **[US Boxed Warnings]: Should be administered under the supervision of a physician experienced in the use of antimetabolite therapy.**

• Intrathecal safety: When used for intrathecal administration, should not be prepared during the preparation of any other agents. After preparation, store intrathecal medications in an isolated location or container clearly marked with a label identifying as "intrathecal" use only. Delivery of intrathecal medications to the patient should only be with other medications intended for administration into the central nervous system (Jacobson 2009).

• Methotrexate overexposure: Glucarpidase is an enzyme that rapidly hydrolyzes extracellular methotrexate into inactive metabolites, allowing for a rapid reduction of methotrexate concentrations. Glucarpidase may be used for methotrexate overexposure; it is approved for the treatment of toxic plasma methotrexate concentrations (>1 micromole/L) in patients with delayed clearance due to renal impairment. Refer to Glucarpidase monograph.

Metabolism/Transport Effects

Substrate of BCRP, OAT3, P-glycoprotein, SLCO1B1

Drug Interactions

(For additional information: Launch drug interactions program) Lexicomp®

Acitretin: May enhance the hepatotoxic effect of Methotrexate. *Risk X: Avoid combination*

Alitretinoin (Systemic): May enhance the hepatotoxic effect of Methotrexate. *Risk C: Monitor therapy*

BCG (Intravesical): Immunosuppressants may diminish the therapeutic effect of BCG (Intravesical). *Risk X: Avoid combination*

BCG (Intravesical): Myelosuppressive Agents may diminish the therapeutic effect of BCG (Intravesical). *Risk X: Avoid combination*

Bile Acid Sequestrants: May decrease the absorption of Methotrexate. *Risk C: Monitor therapy*

Cephalothin: May diminish the therapeutic effect of Methotrexate. *Risk C: Monitor therapy*

Ciprofloxacin (Systemic): May increase the serum concentration of Methotrexate. *Risk C: Monitor therapy*

CloZAPine: Myelosuppressive Agents may enhance the adverse/toxic effect of CloZAPine. Specifically, the risk for neutropenia may be increased. *Risk C: Monitor therapy*

Coccidioides immitis Skin Test: Immunosuppressants may diminish the diagnostic effect of Coccidioides immitis Skin Test. *Risk C: Monitor therapy*

CycloSPORINE (Systemic): May increase the serum concentration of Methotrexate. This may result in nausea, vomiting, oral ulcers, hepatotoxicity and/or nephrotoxicity. Methotrexate may increase the serum concentration of CycloSPORINE (Systemic). This may result in nephrotoxicity. *Risk D: Consider therapy modification*

Deferiprone: Myelosuppressive Agents may enhance the neutropenic effect of Deferiprone. *Risk X: Avoid combination*

Denosumab: May enhance the adverse/toxic effect of Immunosuppressants. Specifically, the risk for serious infections may be increased. *Risk C: Monitor therapy*

Dexketoprofen: May increase the serum concentration of Methotrexate. Management: Concurrent use of dexketoprofen with methotrexate doses of 15 mg/week or more is inadvisable. Use with lower methotrexate doses should only be performed with caution and increased monitoring. *Risk D: Consider therapy modification*

Diethylamine Salicylate: May increase the serum concentration of Methotrexate. *Risk C: Monitor therapy*

Dipyrone: Methotrexate may enhance the adverse/toxic effect of Dipyrone. Specifically, the risk for agranulocytosis and pancytopenia may be increased. Dipyrone may enhance the adverse/toxic effect of Methotrexate. *Risk X: Avoid combination*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Eltrombopag: May increase the serum concentration of OATP1B1/SLCO1B1 Substrates. *Risk C: Monitor therapy*

Fingolimod: Immunosuppressants may enhance the immunosuppressive effect of Fingolimod. Management: Avoid the concomitant use of fingolimod and other immunosuppressants when possible. If combined, monitor patients closely for additive immunosuppressant effects (eg, infections). *Risk D: Consider therapy modification*

Foscarnet: May enhance the nephrotoxic effect of Methotrexate. *Risk X: Avoid combination*

Fosphenytoin-Phenytoin: Methotrexate may decrease the serum concentration of Fosphenytoin-Phenytoin. Fosphenytoin-Phenytoin may increase the serum concentration of Methotrexate. Specifically, fosphenytoin-phenytoin may displace methotrexate from serum proteins, increasing the concentration of free, unbound drug. *Risk C: Monitor therapy*

Gemfibrozil: May increase the serum concentration of OATP1B1/SLCO1B1 Substrates. See separate drug interaction monographs for agents listed as exceptions. *Risk C: Monitor therapy*

Ibrutinib: May increase the serum concentration of Methotrexate. *Risk C: Monitor therapy*

Leflunomide: Methotrexate may enhance the adverse/toxic effect of Leflunomide. Particular concerns are an increased risk of pancytopenia and/or hepatotoxicity. *Risk C: Monitor therapy*

Lenograstim: Antineoplastic Agents may diminish the therapeutic effect of Lenograstim. *Risk D: Consider therapy modification*

LevETIRAcetam: May increase the serum concentration of Methotrexate. *Risk C: Monitor therapy*

Loop Diuretics: Methotrexate may diminish the therapeutic effect of Loop Diuretics. Loop Diuretics may increase the serum concentration of Methotrexate. Methotrexate may increase the serum concentration of Loop Diuretics. Management: Monitor for increased methotrexate and/or loop diuretic levels/toxicity with concomitant use of these agents and monitor for decreased therapeutic effects of loop diuretics. Methotrexate and/or loop diuretic dose reductions may be necessary. *Risk D: Consider therapy modification*

Lumacaftor: May decrease the serum concentration of P-glycoprotein/ABCB1 Substrates. Lumacaftor may increase the serum concentration of P-glycoprotein/ABCB1 Substrates. *Risk C: Monitor therapy*

Mipomersen: May enhance the hepatotoxic effect of Methotrexate. *Risk C: Monitor therapy*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Nivolumab: Immunosuppressants may diminish the therapeutic effect of Nivolumab. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May increase the serum concentration of Methotrexate. Management: Alternative anti-inflammatory therapy should be considered whenever possible, especially if the patient is receiving higher, antineoplastic doses of methotrexate. *Risk D: Consider therapy modification*

Ocrelizumab: May enhance the immunosuppressive effect of Immunosuppressants. *Risk C: Monitor therapy*

Palifermin: May enhance the adverse/toxic effect of Antineoplastic Agents. Specifically, the duration and severity of oral mucositis may be increased. Management: Do not administer palifermin within 24 hours before, during infusion of, or within 24 hours after administration of myelotoxic chemotherapy. *Risk D: Consider therapy modification*

Penicillins: May increase the serum concentration of Methotrexate. *Risk C: Monitor therapy*

P-glycoprotein/ABCB1 Inducers: May decrease the serum concentration of P-glycoprotein/ABCB1 Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-glycoprotein/ABCB1 Inhibitors: May increase the serum concentration of P-glycoprotein/ABCB1 Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Pimecrolimus: May enhance the adverse/toxic effect of Immunosuppressants. *Risk X: Avoid combination*

Probenecid: May increase the serum concentration of Methotrexate. Management: Avoid concomitant use of probenecid and methotrexate if possible. If used together, consider lower methotrexate doses and monitor for evidence of methotrexate toxicity. *Risk D: Consider therapy modification*

Promazine: May enhance the myelosuppressive effect of Myelosuppressive Agents. *Risk C: Monitor therapy*

Proton Pump Inhibitors: May increase the serum concentration of Methotrexate. *Risk C: Monitor therapy*

Ranolazine: May increase the serum concentration of P-glycoprotein/ABCB1 Substrates. *Risk C: Monitor therapy*

Roflumilast: May enhance the immunosuppressive effect of Immunosuppressants. *Risk D: Consider therapy modification*

Salicylates: May increase the serum concentration of Methotrexate. Salicylate doses used for

prophylaxis of cardiovascular events are not likely to be of concern. *Risk D: Consider therapy modification*

Sapropterin: Methotrexate may decrease the serum concentration of Sapropterin. Specifically, methotrexate may decrease tissue concentrations of tetrahydrobiopterin. *Risk C: Monitor therapy*

Sipuleucel-T: Immunosuppressants may diminish the therapeutic effect of Sipuleucel-T. *Risk C: Monitor therapy*

SulfaSALAzine: May enhance the hepatotoxic effect of Methotrexate. *Risk C: Monitor therapy*

Sulfonamide Derivatives: May enhance the adverse/toxic effect of Methotrexate. Management: Consider avoiding concomitant use of methotrexate and either sulfamethoxazole or trimethoprim. If used concomitantly, monitor for the development of signs and symptoms of methotrexate toxicity (eg, bone marrow suppression). *Risk D: Consider therapy modification*

Tacrolimus (Topical): May enhance the adverse/toxic effect of Immunosuppressants. *Risk X: Avoid combination*

Tegafur: Methotrexate may enhance the adverse/toxic effect of Tegafur. *Risk C: Monitor therapy*

Teriflunomide: May increase the serum concentration of OAT3 Substrates. *Risk C: Monitor therapy*

Teriflunomide: May increase the serum concentration of OATP1B1/SLCO1B1 Substrates. *Risk C: Monitor therapy*

Tertomotide: Immunosuppressants may diminish the therapeutic effect of Tertomotide. *Risk C: Monitor therapy*

Theophylline Derivatives: Methotrexate may increase the serum concentration of Theophylline Derivatives. *Risk C: Monitor therapy*

Tofacitinib: Methotrexate may enhance the immunosuppressive effect of Tofacitinib. Management: Avoid the use of tofacinib in combination with potent immunosuppressive methotrexate-containing regimens. *Risk C: Monitor therapy*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Trimethoprim: May enhance the adverse/toxic effect of Methotrexate. Management: Consider avoiding concomitant use of methotrexate and either sulfamethoxazole or trimethoprim. If used concomitantly, monitor for the development of signs and symptoms of methotrexate toxicity (e.g., bone marrow suppression). *Risk D: Consider therapy modification*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). Management: Vaccine efficacy may be reduced. Complete all age-appropriate vaccinations at least 2 weeks prior to starting an immunosuppressant. If vaccinated during immunosuppressant therapy, revaccinate at least 3 months after immunosuppressant discontinuation. *Risk D: Consider therapy modification*

Vaccines (Live): Methotrexate may enhance the adverse/toxic effect of Vaccines (Live). Methotrexate may diminish the therapeutic effect of Vaccines (Live). Management: Low-dose methotrexate (0.4 mg/kg/week or less) is not considered sufficiently immunosuppressive to create vaccine safety concerns. Higher doses of methotrexate should be avoided. *Risk D: Consider therapy modification*

Food Interactions

Methotrexate peak serum levels may be decreased if taken with food. Milk-rich foods may decrease methotrexate absorption. Management: Administer without regard to food.

Pregnancy Risk Factor

X (psoriasis, rheumatoid arthritis) (show table)

Pregnancy Implications

[US Boxed Warning]: Methotrexate has been reported to cause fetal death and/or congenital abnormalities. Methotrexate 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. Some products are contraindicated in pregnant women. Studies in animals and pregnant women have shown evidence of fetal abnormalities; therefore, the manufacturer classifies methotrexate as pregnancy category X (for psoriasis or RA). A pattern of congenital malformations associated with maternal methotrexate use is referred to as the aminopterin/methotrexate syndrome. Features of the syndrome include CNS, skeletal, and cardiac abnormalities. Low birth weight and developmental delay have also been reported. The use of methotrexate may impair fertility and cause menstrual irregularities or oligospermia during treatment and following therapy. Methotrexate is approved for the treatment of trophoblastic neoplasms (gestational choriocarcinoma, chorioadenoma destruens, and hydatidiform mole) and has been used for the medical management of ectopic pregnancy and the medical management of abortion. Pregnancy should be excluded prior to therapy in women of childbearing potential. Use for the treatment of neoplastic diseases only when the potential benefit to the mother outweighs the possible risk to the fetus. Pregnancy should be avoided for ≥3 months following treatment in male patients and ≥1 ovulatory cycle in female patients. A registry is available for pregnant women exposed to autoimmune medications including methotrexate. For additional information contact the Organization of Teratology Information Specialists, OTIS Autoimmune Diseases Study, at 877-311-8972.

Breast-Feeding Considerations

Low amounts of methotrexate are excreted into breast milk. Due to the potential for serious adverse reactions in a breast-feeding infant, use is contraindicated in nursing mothers.

Dietary Considerations

Some products may contain sodium.

Monitoring Parameters

Oncologic uses: Baseline and frequently during treatment: CBC with differential and platelets, serum creatinine, BUN, liver function tests (LFTs); methotrexate levels and urine pH (with high-dose methotrexate); closely monitor fluid and electrolyte status in patients with impaired methotrexate elimination; chest x-ray (baseline); pulmonary function test (if methotrexate-induced lung disease suspected); monitor carefully for toxicities (due to impaired elimination) in patients with ascites, pleural effusion, decreased folate stores, renal impairment, and/or hepatic impairment

Psoriasis (Kalb, 2009; Menter, 2009):

CBC with differential and platelets (baseline, 7 to 14 days after initiating therapy or dosage increase, every 2 to 4 weeks for first few months, then every 1 to 3 months depending on leukocyte count and stability of patient) monitor more closely in patients with risk factors for hematologic toxicity (eg, renal insufficiency, advanced age, hypoalbuminemia); BUN and serum creatinine (baseline and every 2 to 3 months) calculate glomerular filtration rate if at risk for renal dysfunction; consider PPD for latent TB screening (baseline); LFTs (baseline, monthly for first 6 months, then every 1 to 2 months; more frequently if at risk for hepatotoxicity or if clinically indicated; liver function tests should be performed at least 5 days after the last dose); pregnancy test (if female of reproductive

potential); chest x-ray (baseline if underlying lung disease); pulmonary function test (if methotrexate-induced lung disease suspected)

Liver biopsy for patients **with** risk factors for hepatotoxicity: Baseline or after 2 to 6 months of therapy and with each 1 to 1.5 g cumulative dose interval

Liver biopsy for patients **without** risk factors for hepatotoxicity: If persistent elevations in 5 of 9 AST levels during a 12-month period, or decline of serum albumin below the normal range with normal nutritional status. Consider biopsy after cumulative dose of 3.5 to 4 g and after each additional 1.5 g.

Rheumatoid arthritis:

CBC with differential and platelets, serum creatinine, and LFTs: Baseline and every 2 to 4 weeks for 3 months after initiation or following dose increases, then every 8 to 12 weeks during 3 to 6 months of treatment, followed by every 12 weeks beyond 6 months of treatment; monitor more frequently if clinically indicated (Singh [ACR 2016]).

Chest x-ray (within 1 year prior to initiation), Hepatitis B and C serology (if at high risk); tuberculosis testing annually for patients who live, travel or work in areas with likely TB exposure (Kremer 1994).

Liver biopsy: Baseline (consider only for patients with persistent abnormal baseline LFTs, history of alcoholism, or chronic hepatitis B or C) or during treatment if persistent LFT elevations (6 of 12 tests abnormal over 1 year or 5 of 9 results when LFTs performed at 6-week intervals) (Kremer 1994).

Crohn disease (off-label use; Lichtenstein, 2009): CBC with differential and platelets (baseline and periodic) and liver function tests (baseline and every 1 to 2 months); baseline liver biopsy (in patients with abnormal baseline LFTs or with chronic liver disease); liver biopsy at 1 year if (over a 1-year span) AST consistently elevated or serum albumin consistently decreased; chest x-ray (baseline)

Ectopic pregnancy (off-label use; Barnhart, 2009): Prior to therapy, measure serum hCG, CBC with differential and platelets, liver function tests, serum creatinine. Serum hCG concentrations should decrease between treatment days 4 and 7. If hCG decreases by >15%, additional courses are not needed however, continue to measure hCG weekly until no longer detectable. If <15% decrease is observed, repeat dose per regimen.

Reference Range Therapeutic levels: Variable; Toxic concentration: Variable; therapeutic range is dependent upon therapeutic approach.

High-dose regimens produce drug levels that are between 0.1 to 1 micromole/L 24 to 72 hours after drug infusion

Toxic: Low-dose therapy: >0.2 micromole/L; high-dose therapy: >1 micromole/L

Mechanism of Action Methotrexate is a folate antimetabolite that inhibits DNA synthesis, repair, and cellular replication. Methotrexate irreversibly binds to and inhibits dihydrofolate reductase, inhibiting the formation of reduced folates, and thymidylate synthetase, resulting in inhibition of purine and thymidylic acid synthesis, thus interfering with DNA synthesis, repair, and cellular replication. Methotrexate is cell cycle specific for the S phase of the cycle. Actively proliferative tissues are more susceptible to the effects of methotrexate.

The MOA in the treatment of rheumatoid arthritis is unknown, but may affect immune function. In psoriasis, methotrexate is thought to target rapidly proliferating epithelial cells in the skin.

In Crohn disease, it may have immune modulator and anti-inflammatory activity.

Pharmacodynamics/Kinetics

Onset of action: Antirheumatic: 3 to 6 weeks; additional improvement may continue longer than 12 weeks

Absorption:

Oral: Highly variable; dose dependent; decreased absorption at higher doses (pediatric patients: >40 mg/m^2; adult patients: >80 mg/m^2); possibly due to saturation effect

IM injection: Complete

Distribution: Penetrates slowly into third space fluids (eg, pleural effusions, ascites), exits slowly from these compartments (slower than from plasma); sustained concentrations retained in kidney and liver

V_d: IV: 0.18 L/kg (initial); 0.4 to 0.8 L/kg (steady state)

Protein binding: ~50%

Metabolism: Partially metabolized by intestinal flora (after oral administration) to DAMPA by carboxypeptidase; hepatic aldehyde oxidase converts methotrexate to 7-hydroxy methotrexate; polyglutamates are produced intracellularly and are just as potent as methotrexate; their production is dose- and duration-dependent and they are slowly eliminated by the cell once formed. Polyglutamated forms can be converted back to methotrexate.

Bioavailability: Oral: Children: Highly variable: 23% to 95%; Adults: Low doses (≤30 mg/m^2): ~60%; in general, bioavailability is dose dependent and decreases as the dose increases (especially at doses >80 mg/m^2)

Half-life elimination:

Children: ALL: 0.7 to 5.8 hours (dose range: 6.3 to 30 mg/m^2); JIA: 0.9 to 2.3 hours (dose range: 3.75 to 26.2 mg/m^2)

Adults: Low dose: 3 to 10 hours; High dose: 8 to 15 hours

Time to peak, serum: Oral: Children: 0.67 to 4 hours (reported for a 15 mg/m2 dose); Adults: 1 to 2 hours; IM: Children and Adults: 30 to 60 minutes

Excretion: Dose and route dependent; IV: Urine (80% to 90% as unchanged drug; 5% to 7% as 7-hydroxy methotrexate); feces (<10%)

Pricing: US

Solution (Methotrexate Sodium (PF) Injection)

1 g/40mL (40 mL): $41.16

50 mg/2 mL (2 mL): $4.90

100 mg/4 mL (4 mL): $7.32

200 mg/8 mL (8 mL): $10.20

250 mg/10 mL (10 mL): $11.17

Solution (Methotrexate Sodium Injection)

50 mg/2 mL (2 mL): $8.59

250 mg/10 mL (10 mL): $40.31

Solution (reconstituted) (Methotrexate Sodium Injection)

1 g (1): $76.32

Solution Auto-injector (Otrexup Subcutaneous)

7.5 mg/0.4 mL (0.4 mL): $176.82

10 mg/0.4 mL (0.4 mL): $176.82

12.5 mg/0.4 mL (0.4 mL): $176.82

15 mg/0.4 mL (0.4 mL): $176.82

17.5 mg/0.4 mL (0.4 mL): $176.82

20 mg/0.4 mL (0.4 mL): $176.82

22.5 mg/0.4 mL (0.4 mL): $176.82

25 mg/0.4 mL (0.4 mL): $176.82

Solution Auto-injector (Rasuvo Subcutaneous)

7.5 mg/0.15 mL (0.15 mL): $0.00

10 mg/0.2 mL (0.2 mL): $0.00

12.5 mg/0.25 mL (0.25 mL): $0.00

15 mg/0.3 mL (0.3 mL): $141.00

17.5 mg/0.35ml (0.35 mL): $141.00

20 mg/0.4 mL (0.4 mL): $141.00

22.5 mg/0.45ml (0.45 mL): $0.00

25 mg/0.5 mL (0.5 mL): $0.00

27.5 mg/0.55ml (0.55 mL): $0.00

30 mg/0.6 mL (0.6 mL): $0.00

Tablets (Methotrexate Oral)

2.5 mg (100): $356.40

Tablets (Trexall Oral)

5 mg (30): $478.80

7.5 mg (30): $718.26

10 mg (30): $957.66

15 mg (30): $1436.52

Disclaimer: The pricing data provide a representative AWP and/or AAWP price from a single manufacturer of the brand and/or generic product, respectively. The pricing data should be used for benchmarking purposes only, and as such should not be used to set or adjudicate any prices for reimbursement or purchasing functions. Pricing data is updated monthly.

International Brand Names

Abitrexate (IL, SG, TH, TW, ZW); Alltrex (LK); Artrait (AR, PE); Atrexel (MX); Bertanel (ES); Biotrexate (IN); Brimexate (IT); Canceren (KR); Cytotrex (LK); Ebetrex (LV); Ebetrexat (AE, AT, BG, HR, LB); Emthexat (SE); Emthexate (AT, BE, GR, ID, JO, KW, MY, NL, PH, PK, PT, TH, TR, TW); Emthexate PF (KR); Emthrxate (SI); Hytas (BR); Imutrex (LK); Lantarel (DE); Ledertrexate (BE, FR, LU, MX, NZ, PT); Maxtrex (GB); Medsatrexate (MX); Meisusheng (CN); Merox-50 (ET); Metex (LV); Methoblastin (AU, NZ); Methotrexat (HR); Methotrexat Bigmar (CH); Methotrexat Ebewe (HU); Methotrexat Farmos (CH); Methotrexat Lachema (HU); Methotrexat Lederle (CH); Methotrexat Teva (CH); Methotrexate (AU, HK, ID, IL, MY, PH, TH, TW); Methotrexate Faulding (SE); Methotrexate Pharmacia (SE); Methotrexate Wyeth Lederle (SE); Methotrexate ”Lederle” (HU); Methotrexate[inj.] (HR, IT); Methotrexato (AR, EC); Methox (BD); Metodik (AR); Metoject (CZ, DK, ES, FR, HR, RO, SK); Metotreksat (HR); Metotressato Teva (IT); Metotrexato (CL); Metotrexato DBL (IT); Metrex (LK, PY); Mexat (CO); Midu (CN); Mtrex (BD); MTX Hexal (LU); Neotrexate (IN); Novatrex (FR); Onkomet (TH); Otaxem (MX); P&U Methotrexate (ZA); Pterin (PH); Quinux (ES); Reumatrex (PE); Sanotrexat (ID); Texate (MX); Texorate (ID); Trexan (EE, FI, HN, HU, LT, PL, RU, SG, TR, TW); Trexol (LK); Trexonate (BD); Trexxol (ET); Trixilem (CL, MX, TH); Unitrexates (VN); Viztreksat (UA); Xantromid (PY); Zexate (ET, PH, UY, VE, VN, ZW)

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