

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use METHOTREXATE INJECTION safely and effectively. See full prescribing information for METHOTREXATE INJECTION.

METHOTREXATE injection, for intravenous use

Initial U.S. Approval: 1953

WARNING: EMBRYO-FETAL TOXICITY, HYPERSENSITIVITY REACTIONS and OTHER SERIOUS ADVERSE REACTIONS

See full prescribing information for complete boxed warning.

- Methotrexate Injection can cause embryo-fetal toxicity, including fetal death. Advise females and males of reproductive potential to use effective contraception during and after treatment with Methotrexate Injection. (4, 5.1, 8.1, 8.3)
- Methotrexate Injection is contraindicated in patients with a history of severe hypersensitivity reactions to methotrexate, including anaphylaxis (4, 5.2).
- Serious adverse reactions, including death, have been reported with methotrexate. Closely monitor for infections and adverse reactions of the nervous system, kidneys, liver, bone marrow, gastrointestinal tract, lungs, and skin. Withhold or discontinue Methotrexate Injection as appropriate (5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 5.10).

INDICATIONS AND USAGE

Methotrexate Injection is a folate analog metabolic inhibitor indicated for the treatment of:

- adult and pediatric patients with acute lymphoblastic leukemia (ALL) as part of a combination chemotherapy regimen (1.1).
- adult and pediatric patients with non-Hodgkin lymphoma (1.2).
- adult and pediatric patients with osteosarcoma as part of a combination chemotherapy regimen (1.3).
- **Limitations of Use:** Methotrexate Injection is not indicated for non-oncology diseases (1.4).

DOSAGE AND ADMINISTRATION

- **For intravenous use only. Not for intrathecal use.**
- Methotrexate Injection is available as a solution at a concentration of 5 grams/50 mL (100 mg/mL). Verify the concentration prior to preparation and administration to avoid overdosage (2.1).
- Verify pregnancy status in females of reproductive potential before starting Methotrexate Injection. (2.1, 4, 5.1)
- See full prescribing information about monitoring and concomitant therapies for intermediate- and high-dose regimens (2.2).
- **Acute Lymphoblastic Leukemia:** The recommended dosage of Methotrexate Injection varies from 10 mg/m² to 5000 mg/m² intravenously as part of a combination chemotherapy regimen (2.3).
- **Non-Hodgkin Lymphoma:** The recommended dosage of Methotrexate Injection varies from 1000 mg/m² to 8000 mg/m² intravenously (2.4).
- **Osteosarcoma:** The recommended dosage of Methotrexate Injection is typically 12 grams/m² (maximum: 20 grams per dose) as an intravenous infusion over 4 hours followed by leucovorin rescue in accordance with high-

dose methotrexate regimen guidelines. Adjust subsequent doses based on observed peak serum methotrexate concentrations as appropriate (2.5).

DOSAGE FORMS AND STRENGTHS

Injection: 5 grams/50 mL (100 mg/mL), clear orange-yellow, isotonic, sterile, preservative-free solution in single-dose vial

CONTRAINDICATIONS

- History of severe hypersensitivity to methotrexate (4)

WARNINGS AND PRECAUTIONS

- **Serious Infections:** Monitor patients for infection during and after treatment with Methotrexate Injection. Withhold or discontinue Methotrexate Injection for serious infections as appropriate (5.9).
- **Secondary Malignancies:** Can occur with methotrexate (5.12).
- **Tumor Lysis Syndrome:** Institute appropriate prophylactic measures in patients at risk for tumor lysis syndrome prior to initiation of Methotrexate Injection (5.13).
- **Immunizations and Risks Associated with Live Vaccines:** Immunization may be ineffective. Live vaccines are not recommended due to risk of disseminated infection (5.14).
- **Infertility:** Can cause impairment of fertility, oligospermia, and menstrual dysfunction. (5.15, 8.3)

ADVERSE REACTIONS

Common adverse reactions include: ulcerative stomatitis, leukopenia, nausea and abdominal distress (6).

To report SUSPECTED ADVERSE REACTIONS, contact Accord Healthcare Inc. at 1-866-941-7875 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Refer to the full prescribing information for information about drug interactions with methotrexate (7).

USE IN SPECIFIC POPULATIONS

- **Lactation:** Advise not to breastfeed (8.2).
- **Pediatric use:** Methotrexate can cause serious neurotoxicity in patients with acute lymphoblastic leukemia. (8.4)
- **Renal Impairment:** Consider reducing the dose or discontinuing Methotrexate Injection for renal impairment as appropriate (8.6).
- **Hepatic Impairment:** Consider reducing the dose or discontinuing Methotrexate Injection for hepatic impairment as appropriate (8.7).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 3/2022

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FULL PRESCRIBING INFORMATION

WARNING: EMBRYO-FETAL TOXICITY, HYPERSENSITIVITY REACTIONS and OTHER SERIOUS ADVERSE REACTIONS

- **Methotrexate Injection can cause embryo-fetal toxicity, including fetal death. Advise females and males of reproductive potential to use effective contraception [see Contraindications (4), Warnings and Precautions (5.1), and Use in Specific Populations (8.1, 8.3)].**
- **Methotrexate Injection is contraindicated in patients with a history of severe hypersensitivity reactions to methotrexate, including anaphylaxis [see Contraindications (4) and Warnings and Precautions (5.2)].**
- **Other serious adverse reactions, including death, have been reported with methotrexate. Closely monitor for infections and adverse reactions of the nervous system, kidneys, liver, bone marrow, gastrointestinal tract, lungs, and skin. Withhold or discontinue Methotrexate Injection as appropriate [see Warnings and Precautions (5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 5.10)].**

1 INDICATIONS AND USAGE

1.1 Acute Lymphoblastic Leukemia

Methotrexate Injection is indicated for the treatment of adult and pediatric patients with acute lymphoblastic leukemia (ALL) as part of a combination chemotherapy regimen.

1.2 Non-Hodgkin Lymphoma

Methotrexate Injection is indicated for the treatment of adult and pediatric patients with non-Hodgkin lymphoma.

1.3 Osteosarcoma

Methotrexate Injection is indicated for the treatment of adult and pediatric patients with osteosarcoma as part of a combination chemotherapy regimen.

1.4 Limitations of Use

Methotrexate Injection is not indicated for non-oncology diseases.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Safety Information

For intravenous use only. Not for intrathecal use.

- Methotrexate Injection is available as a preservative-free solution at a concentration of 100 mg/mL. Verify the concentration prior to preparation and administration to avoid overdose.
- Verify pregnancy status in females of reproductive potential before starting Methotrexate Injection [see Contraindications (4) and Warnings and Precautions (5.1)].
- For patients switching between a methotrexate product administered orally and Methotrexate Injection, consider potential differences in bioavailability.

2.2 Recommended Monitoring and Concomitant Therapies to Promote Methotrexate Elimination and Decrease Toxicity for Intermediate- and High-Dose Regimens

To decrease the risk of severe adverse reactions [*see Warnings and Precautions (5)*]:

- Administer leucovorin rescue in patients receiving Methotrexate Injection doses of 500 mg/m² or greater (e.g., high-dose).
- Consider leucovorin rescue for patients receiving Methotrexate Injection doses between 100 mg/m² to less than 500 mg/m² (e.g., intermediate-dose). Refer to the leucovorin prescribing information for additional information.
- For high-dose Methotrexate Injection regimens, follow the supportive care and monitoring instructions below. Also consider for patients receiving intermediate-dose Methotrexate Injection regimens.
 - Monitor serum creatinine, electrolytes, at baseline and at least daily during therapy.
 - Administer intravenous fluids starting before the first dose and continuing throughout treatment to maintain adequate hydration and urine output.
 - Alkalinize urine starting before the first dose and continuing throughout treatment to maintain a urinary pH of 7 or higher.
 - Monitor methotrexate concentrations at least daily and adjust hydration and leucovorin dosing as needed.
 - Administer glucarpidase in patients who have toxic plasma methotrexate concentrations (> 1 micromole per liter) and delayed methotrexate clearance due to impaired renal function (refer to the glucarpidase Prescribing Information for additional information)

2.3 Recommended Dosage for Acute Lymphoblastic Leukemia

Methotrexate Injection is used as part of a multi-drug regimen. The recommended dosage varies from 10 to 5000 mg/m² intravenously. For high dose Methotrexate Injection regimens, use leucovorin rescue in accordance with high-dose methotrexate regimen guidelines [*see Dosage and Administration (2.2)*]. Individualize the dose and schedule of Methotrexate Injection based on disease state, patient risk category, concurrent drugs used, phase of treatment, and response to treatment.

2.4 Recommended Dosage for Non-Hodgkin Lymphoma

The recommended dosage of Methotrexate Injection varies. When used in combination, recommended dosages range from 1000 mg/m² to 8000 mg/m² intravenously. When used as a single agent, a recommended dosage is 8,000 mg/m² intravenously for central nervous system-directed therapy.

As part of a combination chemotherapy regimen, a recommended dosage of Methotrexate Injection is 1,000 mg/m² or 3,000 mg/m² as an intravenous infusion over 24 hours followed by leucovorin rescue in accordance with high-dose methotrexate regimen guidelines [*see Dosage and Administration (2.2)*].

For central nervous system-directed therapy, a recommended dosage of Methotrexate Injection is 8,000 mg/m² as an intravenous infusion over 4 hours as a single agent or in combination with immunochemotherapy at doses ranging from 3,000 mg/m² to 8,000 mg/m² followed by leucovorin

rescue in accordance with high-dose methotrexate regimen guidelines [see *Dosage and Administration (2.2)*].

Individualize the dose and schedule of Methotrexate Injection based on disease state, patient risk category, concurrent drugs, treatment phase and treatment response.

2.5 Recommended Dosage for Osteosarcoma

The recommended dosage of Methotrexate Injection is typically 12 **grams**/m² (maximum: 20 **grams** per dose) as an intravenous infusion over 4 hours administered as a component of a combination chemotherapy regimen. Administer leucovorin rescue in accordance with high-dose methotrexate regimen guidelines [see *Dosage and Administration (2.2)*]. Subsequent doses may need to be adjusted based on observed peak serum methotrexate concentrations. Dosage and schedule may vary based upon factors such as patient comorbidities, disease state, and prior treatments.

2.6 Dosage Modifications for Adverse Reactions

Discontinue Methotrexate Injection for

- Anaphylaxis or other severe hypersensitivity reactions [see *Warnings and Precautions (5.2)*].
- Lymphoproliferative disease [see *Warnings and Precautions (5.12)*]

Withhold, dose reduce or discontinue Methotrexate Injection as appropriate for:

- Myelosuppression [see *Warnings and Precautions (5.3)*]

Withhold or discontinue Methotrexate Injection as appropriate for:

- Serious infections [see *Warnings and Precautions (5.4)*]
- Renal toxicity [see *Warnings and Precautions (5.5)*]
- Hepatotoxicity [see *Warnings and Precautions (5.6)*]
- Neurotoxicity [see *Warnings and Precautions (5.7)*]
- Gastrointestinal toxicity [see *Warnings and Precautions (5.8)*]
- Pulmonary toxicity [see *Warnings and Precautions (5.9)*]
- Dermatologic reactions [see *Warnings and Precautions (5.10)*]

2.7 Preparation

- **Methotrexate Injection is available as a solution at a concentration of a 100 mg/mL. Verify the concentration prior to preparation and administration to avoid overdose.**
- Methotrexate Injection is a hazardous drug. Follow applicable special handling and disposable procedures.¹
- Methotrexate Injection may be further diluted immediately before use with an appropriate sterile, preservative-free medium such as 5% Dextrose Solution, USP or 0.9% Sodium Chloride Injection, USP.
- Visually inspect for particulate matter and discoloration prior to administration. Discard if particulate matter or discoloration is observed.

3 DOSAGE FORMS AND STRENGTHS

Injection: 5 grams/50 mL (100 mg/mL), clear orange-yellow, isotonic, sterile, preservative-free solution in single-dose vial.

4 CONTRAINDICATIONS

Methotrexate Injection is contraindicated in patients with a history of severe hypersensitivity to methotrexate [*see Warnings and Precautions (5.2)*].

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

Based on published reports and its mechanism of action, methotrexate can cause embryo-fetal toxicity, including fetal death when administered to a pregnant woman.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Methotrexate Injection and for 6 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with Methotrexate Injection and for 3 months after the final dose [*see Contraindications (4) and Use in Specific Populations (8.1, 8.3, 8.4)*].

5.2 Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis, can occur with methotrexate [*see Adverse Reactions (6)*]. If signs or symptoms of anaphylaxis or any other serious hypersensitivity reaction occurs, immediately discontinue Methotrexate Injection and institute appropriate therapy [*see Dosage and Administration (2.6), Contraindications (4)*].

5.3 Myelosuppression

Methotrexate suppresses hematopoiesis and can cause severe and life-threatening pancytopenia, aplastic anemia, leukopenia, neutropenia, and thrombocytopenia [*see Dosage and Administration (2.6), Adverse Reactions (6)*].

Obtain blood counts at baseline and periodically during treatment. Monitor patients for possible clinical complications of myelosuppression. Provide supportive care and withhold, reduce dose, or discontinue Methotrexate Injection as needed [*see Dosage and Administration (2.6)*].

5.4 Serious Infections

Patients treated with methotrexate are at increased risk for developing life-threatening or fatal bacterial, fungal, or viral infections including opportunistic infections such as *Pneumocystis jiroveci* pneumonia, invasive fungal infections, hepatitis B reactivation, tuberculosis primary infection or reactivation, and disseminated *Herpes zoster* and cytomegalovirus.

Closely monitor patients for the development of signs and symptoms of infection during and after treatment with Methotrexate Injection. Withhold or discontinue Methotrexate Injection in patients who develop serious infections [*see Dosage and Administration (2.6)*].

5.5 Renal Toxicity

Methotrexate can cause renal toxicity including irreversible acute renal failure. Monitor renal function and withhold or discontinue methotrexate as needed for severe renal toxicity.

For patients receiving high-dose regimens, follow recommendations to decrease the risk of renal

injury and mitigate renal toxicity [*see Dosage and Administration (2.2)*].

Patients with impaired renal function are at increased risk for methotrexate toxicity [*see Use in Specific Populations (8.6)*].

Consider administration of glucarpidase in patients with toxic plasma methotrexate concentrations (>1 micromole per liter) and delayed clearance due to impaired renal function. [*see Dosage and Administration (2.2)*].

5.6 Hepatotoxicity

Methotrexate can cause severe and potentially irreversible hepatotoxicity, including fibrosis, cirrhosis, and fatal liver failure [*see Adverse Reactions (6)*].

The safety of Methotrexate Injection in patients with liver disease is unknown. Avoid use of Methotrexate Injection in patients with chronic liver disease, unless benefits clearly outweigh the risks. The risk of hepatotoxicity is increased with heavy alcohol consumption.

Assess liver function prior to initiating Methotrexate Injection and monitor liver function tests during treatment. Withhold or discontinue Methotrexate Injection as appropriate [*see Dosage and Administration (2.6)*].

5.7 Neurotoxicity

Methotrexate can cause severe acute and chronic neurotoxicity, which can be progressive, irreversible, and fatal.

Serious neurotoxicity, including generalized and focal seizures, have occurred in pediatric patients [*see Use in Specific Populations (8.4)*].

Leukoencephalopathy

Leukoencephalopathy can occur with intermediate- and high-dose intravenous regimens. The risk of leukoencephalopathy is increased with prior cranial radiation.

Transient Acute Neurologic Syndrome

A transient acute stroke-like syndrome can occur with high-dose methotrexate. Clinical manifestations include confusion, hemiparesis, transient blindness, seizures, and coma.

Monitor patients for neurotoxicity. Withhold or discontinue Methotrexate Injection as appropriate [*see Dosage and Administration (2.7)*].

5.8 Gastrointestinal Toxicity

Methotrexate can cause diarrhea, vomiting, stomatitis, hemorrhagic enteritis and fatal intestinal perforation [*see Adverse Reactions (6)*]. Patients with peptic ulcer disease or ulcerative colitis are at a greater risk of developing severe gastrointestinal adverse reactions.

Withhold or discontinue Methotrexate Injection for severe gastrointestinal toxicity, and institute appropriate supportive care as needed [*see Dosage and Administration (2.6)*].

5.9 Pulmonary Toxicity

Methotrexate-induced pulmonary toxicity including acute or chronic interstitial pneumonitis and irreversible or fatal cases can occur at all dose levels. Monitor patients for signs of pulmonary toxicity and withhold or discontinue Methotrexate Injection as appropriate [*see Dosage and*

Administration (2.6)].

5.10 Dermatologic Reactions

Severe, including fatal dermatologic reactions, such as toxic epidermal necrolysis, Stevens-Johnson syndrome, exfoliative dermatitis, skin necrosis, and erythema multiforme, can occur with methotrexate [*see Adverse Reactions (6)*].

Psoriasis may be aggravated by concomitant exposure to ultraviolet radiation.

Methotrexate can also cause radiation recall dermatitis and photodermatitis (sunburn) reactivation.

Monitor patients for signs of dermatologic toxicity and withhold or permanently discontinue Methotrexate Injection for severe dermatologic adverse reactions. Counsel patients to avoid excessive sun exposure and use sun protection measures.

5.11 Folic Acid Supplementation

Neoplastic Diseases

Products containing folic acid or its derivatives may decrease the clinical effectiveness of methotrexate. Avoid use of products containing folic acid or folinic acid unless clinically indicated [*see Drug Interactions (7.1)*].

5.12 Secondary Malignancies

Secondary malignancies can occur at all dose levels of methotrexate. In some cases, lymphoproliferative disease that occurred during therapy with methotrexate regressed completely following withdrawal of methotrexate. If lymphoproliferative disease occurs, discontinue Methotrexate Injection and institute appropriate treatment if lymphoma does not regress.

5.13 Tumor Lysis Syndrome

Methotrexate can induce tumor lysis syndrome in patients with rapidly growing tumors. Institute appropriate treatment for prevention and management of tumor lysis syndrome.

5.14 Immunization and Risks Associated with Live Vaccines

Immunization during Methotrexate Injection treatment may be ineffective.

Disseminated infections following administration of live vaccines have been reported.

Update immunizations according to immunization guidelines prior to initiating Methotrexate Injection. Immunization with live vaccines is not recommended during treatment. The interval between live vaccinations and initiation of Methotrexate Injection should be in accordance with current vaccination guidelines for patients on immunosuppressive therapies.

5.15 Infertility

Based on published reports, methotrexate can cause impairment of fertility, oligospermia, and menstrual dysfunction. It is not known if the infertility may be reversible in affected patients. Discuss the risk of effects on reproduction with female and male patients of reproductive potential [*see Use in Specific Populations (8.3)*].

5.16 Increased Risk of Adverse Reactions Due to Third-Space Accumulation

Methotrexate can exit slowly from third space accumulations resulting in prolonged terminal plasma half-life and toxicity. Evacuate significant third-space accumulations prior to Methotrexate Injection administration [see *Clinical Pharmacology* (12.3)].

5.17 Increased Risk of Soft Tissue and Bone Toxicity with Concomitant Radiotherapy

Concomitant radiation therapy increases the risk of soft tissue necrosis and osteonecrosis associated with methotrexate.

6 ADVERSE REACTIONS

The following adverse reactions are described, or described in greater detail, in other sections:

- Hypersensitivity Reactions [see *Warnings and Precautions* (5.2)]
- Myelosuppression [see *Warnings and Precautions* (5.3)]
- Serious Infections [see *Warnings and Precautions* (5.4)]
- Renal Toxicity [see *Warnings and Precautions* (5.5)]
- Hepatotoxicity [see *Warnings and Precautions* (5.6)]
- Neurotoxicity [see *Warnings and Precautions* (5.7)]
- Gastrointestinal Toxicity [see *Warnings and Precautions* (5.8)]
- Pulmonary Toxicity [see *Warnings and Precautions* (5.9)]
- Dermatologic Reactions [see *Warnings and Precautions* (5.10)]
- Secondary Malignancies [see *Warnings and Precautions* (5.12)]
- Tumor Lysis Syndrome [see *Warnings and Precautions* (5.13)]
- Increased Risk of Adverse Reactions due to Third Space Accumulation [see *Warnings and Precautions* (5.16)]

The following adverse reactions associated with the use of methotrexate were identified in clinical studies or postmarketing reports. Because some of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Common adverse reactions were: ulcerative stomatitis, leukopenia, nausea, and abdominal distress. Other frequently reported adverse reactions were: infection, malaise, fatigue, chills, fever, and dizziness.

Blood and lymphatic system disorders: aplastic anemia, lymphadenopathy, hypogammaglobulinemia

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

Endocrine disorders: diabetes

Eye disorders: optic neuropathy, blurred vision, ocular irritation, conjunctivitis, xerophthalmia

Gastrointestinal disorders: hemorrhagic enteritis, intestinal perforation, gingivitis, pancreatitis, pharyngitis, hematemesis, melena, gastrointestinal ulceration and bleeding

Hepatobiliary disorders: acute hepatitis, decreased serum albumin, fibrosis, cirrhosis, liver failure

Immune system disorders: anaphylaxis, anaphylactoid reactions, vasculitis

Metabolism: hyperglycemia

Musculoskeletal disorders: Stress fracture, soft tissue necrosis, arthralgia, myalgia, osteoporosis

Nervous system disorders: headaches, drowsiness, blurred vision, speech impairment (including dysarthria and aphasia), transient cognitive dysfunction, mood alteration, unusual cranial sensations, paresis, encephalopathy, leukoencephalopathy, and convulsions.

Renal disorders: Severe renal toxicity including renal failure, azotemia, hematuria, proteinuria, cystitis

Reproductive disorders: defective oogenesis or spermatogenesis, loss of libido, impotence, gynecomastia, menstrual dysfunction

Respiratory disorders: pulmonary fibrosis, respiratory failure, chronic interstitial obstructive pulmonary disease, pleuritic pain and thickening, alveolitis

Skin disorders: toxic epidermal necrolysis, Stevens-Johnson syndrome, exfoliative dermatitis, skin necrosis, and erythema multiforme, erythematous rashes, pruritus, alopecia, skin ulceration, accelerated nodulosis, urticaria, pigmentary changes, ecchymosis, telangiectasia, photosensitivity, acne, furunculosis

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on Methotrexate

Drugs that Increase Methotrexate Exposure

Coadministration of methotrexate with the following products may increase methotrexate plasma concentrations, which may increase the risk of severe adverse reactions to methotrexate.

- Penicillin or sulfonamide antibiotics
- Highly protein-bound drugs (e.g., oral anticoagulants, phenytoin, salicylates, sulfonamides, sulfonyleureas, and tetracyclines)
- Proton pump inhibitors
- Probenecid
- Antifolate drugs (e.g., dapsone, pemetrexed, pyrimethamine and sulfonamides)
- Aspirin and other nonsteroidal anti-inflammatory drugs

Unexpectedly severe and fatal gastrointestinal toxicity can occur with concomitant administration of methotrexate (primarily at high dose) and nonsteroidal anti-inflammatory drugs (NSAIDs)

- Mercaptopurine
- Weak acids (e.g., salicylates)

Increased organ specific adverse reactions may also occur when methotrexate is coadministered with hepatotoxic or nephrotoxic products.

If coadministration cannot be avoided, monitor closely for methotrexate adverse reactions [*see Adverse Reactions (6)*].

Nitrous Oxide

Coadministration of methotrexate with nitrous oxide anesthesia potentiates the effect of methotrexate on folate-dependent metabolic pathways, which may increase the risk of severe methotrexate adverse reactions. Avoid nitrous oxide anesthesia in patients receiving methotrexate. Consider alternative therapies in patients who have received prior nitrous oxide anesthesia.

Folic Acid

Coadministration of methotrexate with folic acid or its derivatives decreases the clinical effectiveness of methotrexate in patients with neoplastic diseases. Methotrexate competes with reduced folates for active transport across cell membranes. Instruct patients to take folic or folinic acid only as directed by their healthcare provider [*see Warnings and Precautions (5.11)*].

7.2 Effects of Methotrexate on Other Drugs

Theophylline

Coadministration of methotrexate with theophylline increases theophylline plasma concentrations which may increase the risk of theophylline adverse reactions. Monitor theophylline levels and adjust the theophylline dosage in accordance with approved product labeling.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on published reports and its mechanism of action, methotrexate can cause embryo-fetal toxicity and fetal death when administered to a pregnant woman [*see Data and Clinical Pharmacology (12.1)*]. There are no animal data that meet current standards for nonclinical developmental toxicity studies. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Human Data

Published data from case reports, literature reviews, and observational studies report that methotrexate exposure during pregnancy is associated with an increased risk of embryo-fetal toxicity and fetal death. Methotrexate exposure during the first trimester of pregnancy is associated with an increased incidence of spontaneous abortions and multiple adverse developmental outcomes, including skull anomalies, facial dysmorphism, central nervous system abnormalities, limb abnormalities, and sometimes cardiac anomalies and intellectual impairment. Adverse outcomes associated with exposure during second and third trimesters of pregnancy include intrauterine growth restriction and functional abnormalities. Because methotrexate is widely distributed and persists in the body for a prolonged period, there is a potential risk to the fetus from preconception methotrexate exposure.

A prospective multicenter study evaluated pregnancy outcomes in women taking methotrexate less than or equal to 30 mg per week after conception. The rate of spontaneous abortion/miscarriage in pregnant women exposed to methotrexate was 42.5% (95% confidence interval [95% CI] 29.2-58.7), which was higher than in unexposed patients with autoimmune disease (22.5%, 95% CI

16.8-29.7) and unexposed patients with non-autoimmune disease (17.3%, 95% CI 13-22.8). Of the live births, the rate of major birth defects in pregnant women exposed to methotrexate after conception was higher than in unexposed patients with autoimmune disease (adjusted odds ratio (OR) 1.8 [95% CI 0.6-5.7]) and unexposed patients with non-autoimmune disease (adjusted OR 3.1 [95% CI 1.03-9.5]) (2.9%). Major birth defects associated with pregnancies exposed to methotrexate after conception were not always consistent with methotrexate-associated adverse developmental outcomes.

8.2 Lactation

Risk Summary

Limited published literature reports the presence of methotrexate in human milk in low amounts, with the highest breast milk to plasma concentration ration reported to be 0.08:1. No information is available on the effects of methotrexate on a breastfed infant or on milk production. Because of the potential for serious adverse reactions from methotrexate in breastfed infants, advise women not to breastfeed during treatment with Methotrexate Injection and for 1 week after the final dose.

8.3 Females and Males of Reproductive Potential

Methotrexate can cause malformations and fetal death at doses less than or equal to the recommended clinical doses [see *Use in Specific Populations (8.1)*].

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating Methotrexate Injection [see *Contraindications (4)* and *Use in Specific Populations (8.1)*].

Contraception

Females

Advise females of reproductive potential to use effective contraception during and for 6 months after the final dose of Methotrexate Injection therapy.

Males

Methotrexate can cause chromosomal damage to sperm cells. Advise males with female partners of reproductive potential to use effective contraception during and for 3 months after the final dose of Methotrexate Injection therapy.

Infertility

Females

Based on published reports of female infertility after therapy with methotrexate, advise females of reproductive potential that Methotrexate Injection can cause impairment of fertility and menstrual dysfunction during and after cessation of therapy. It is not known if the infertility may be reversed in all affected females.

Males

Based on published reports of male infertility after therapy with methotrexate, advise males that Methotrexate Injection can cause oligospermia or infertility during and after cessation of therapy. It is not known if the infertility may be reversed in all affected males.

8.4 Pediatric Use

The safety and effectiveness of Methotrexate Injection in pediatric patients have been established for ALL, non-Hodgkin lymphoma, and osteosarcoma.

Additional risk information is described below.

Leukemia/Lymphoma

Serious neurotoxicity, frequently manifested as generalized or focal seizures, has been reported with unexpectedly increased frequency among pediatric patients with acute lymphoblastic leukemia who were treated with intermediate-dose intravenous methotrexate (1000 mg/m²) [*see Warnings and Precautions (5.7)*].

8.5 Geriatric Use

Clinical studies of methotrexate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

8.6 Renal Impairment

Methotrexate elimination is reduced in patients with renal impairment [creatinine clearance (CL_{cr}) less than 90 mL/min, calculated using Cockcroft-Gault] [*see Clinical Pharmacology (12.3)*]. Patients with renal impairment are at increased risk for methotrexate adverse reactions.

Follow recommendations to promote methotrexate elimination and decrease risk of acute kidney injury and other methotrexate toxicities in patients who are receiving intermediate- or high-dose regimens [*see Dosage and Administration (2.2) and Warnings and Precautions (5.5)*]. Consider reducing the dose or discontinuing Methotrexate Injection in patients with renal impairment as appropriate.

8.7 Hepatic Impairment

The pharmacokinetics and safety of methotrexate in patients with hepatic impairment is unknown. Patients with hepatic impairment may be at increased risk for methotrexate adverse reaction based on elimination characteristics of methotrexate [*see Clinical Pharmacology (12.3)*]. Consider reducing the dose or discontinuing Methotrexate Injection in patients with hepatic impairment as appropriate [*see Warnings and Precautions (5.6)*].

10 OVERDOSAGE

Manifestations

Overdosage, including fatal overdosage, has occurred with methotrexate.

Manifestations of overdosage include adverse reactions reported at pharmacologic doses, particularly hematologic and gastrointestinal reactions (e.g., leukopenia, thrombocytopenia, anemia, pancytopenia, myelosuppression, mucositis, stomatitis, oral ulceration, nausea, vomiting, gastrointestinal ulceration, or gastrointestinal bleeding). In some cases, no symptoms were reported; however, sepsis or septic shock, renal failure, and aplastic anemia were also reported.

Management

Leucovorin and levoleucovorin are indicated to diminish the toxicity and counteract the effect of inadvertently administered overdosages of methotrexate. Administer leucovorin or levoleucovorin as soon as possible after overdosage (refer to the leucovorin or levoleucovorin prescribing

information). Monitor serum methotrexate concentrations closely to guide leucovorin or levoleucovorin therapy. Monitor serum creatinine concentrations closely, because high serum methotrexate concentrations may cause renal damage leading to acute renal failure.

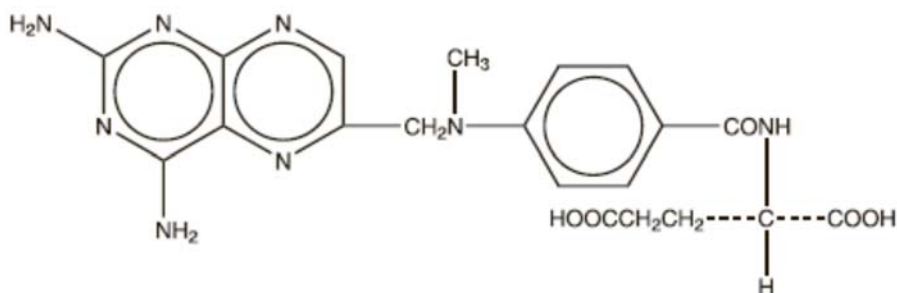
Glucarpidase is indicated for the treatment of toxic methotrexate concentrations in patients with delayed methotrexate clearance due to impaired renal function (refer to the glucarpidase prescribing information). If glucarpidase is used, do not administer leucovorin within two hours before or after a dose of glucarpidase because leucovorin is a substrate for glucarpidase.

Hydration and urinary alkalinization may be necessary to prevent the precipitation of methotrexate and its metabolites in the renal tubules.

Neither hemodialysis nor peritoneal dialysis has been shown to improve methotrexate elimination. However, effective clearance of methotrexate has been reported with acute, intermittent hemodialysis using a high flux dialyzer.

11 DESCRIPTION

Methotrexate is a folate analog metabolic inhibitor with the chemical name of *N*-[4-[(2,4-diamino-6-pteridiny) methyl]methylamino]benzoyl]-L-glutamic acid. The molecular weight is 454.45 g/mol and the molecular formula is C₂₀H₂₂N₈O₅. The structural formula is shown below:



Methotrexate is practically insoluble in water. Therefore, the pH of the methotrexate solution is adjusted to approximately 8.5 with sodium hydroxide in Water for Injection to produce Methotrexate Injection.

Methotrexate Injection for intravenous use is supplied as clear orange-yellow, sterile, preservative-free solution in clear glass single-dose vial sealed with gray rubber stopper and yellow aluminum flip-off seal. Each 100 mg/mL, 50 mL vial contains 5 grams methotrexate and the following inactive ingredient: sodium hydroxide to adjust the pH to approximately 8.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Methotrexate inhibits dihydrofolic acid reductase. Dihydrofolates must be reduced to tetrahydrofolates by this enzyme before they can be utilized as carriers of one-carbon groups in the synthesis of purine nucleotides and thymidylate. Therefore, methotrexate interferes with DNA synthesis, repair, and cellular replication. Actively proliferating tissues such as malignant cells, bone marrow, fetal cells, buccal and intestinal mucosa, and cells of the urinary bladder are in general more sensitive to this effect of methotrexate.

12.3 Pharmacokinetics

Distribution

After intravenous administration, the initial volume of distribution is approximately 0.18 L/kg (18% of body weight) and steady-state volume of distribution is approximately 0.4 L/kg to 0.8 L/kg (40 to 80% of body weight).

Methotrexate competes with reduced folates for active transport across cell membranes by means of a single carrier-mediated active transport process. At serum concentrations greater than 100 micromolar, passive diffusion becomes a major pathway by which effective intracellular concentrations can be achieved.

Methotrexate in serum is approximately 50% protein bound.

Methotrexate may be displaced from plasma albumin by various compounds, including sulfonamides, salicylates, tetracyclines, chloramphenicol, and phenytoin.

Methotrexate does not penetrate the blood-cerebrospinal fluid barrier in therapeutic amounts when given intravenously.

Elimination

The terminal half-life reported for methotrexate is approximately 3 to 10 hours for patients receiving doses less than 30 mg/m².

Following intravenous administration of high-dose methotrexate, the terminal half-life is 8 hours to 15 hours.

Metabolism

Methotrexate undergoes hepatic and intracellular metabolism to polyglutamated forms which can be converted back to methotrexate by hydrolase enzymes. These polyglutamates act as inhibitors of dihydrofolate reductase and thymidylate synthetase. Small amounts of methotrexate polyglutamates may remain in tissues for extended periods. The retention and prolonged drug action of these active metabolites vary among different cells, tissues and tumors. Methotrexate undergoes minor metabolism to 7-hydroxymethotrexate and accumulation may become significant following high dosages. The aqueous solubility of 7-hydroxymethotrexate is 3- to 5-fold lower than the solubility of methotrexate.

Excretion

Renal excretion is the primary route of elimination and is dependent upon dosage and route of administration. With intravenous administration, 80% to 90% of the administered dose is excreted unchanged in the urine within 24 hours. There is limited biliary excretion amounting to 10% or less of the administered dose. Enterohepatic recirculation of methotrexate has been proposed.

Renal excretion occurs by glomerular filtration and active tubular secretion. Nonlinear elimination due to saturation of renal tubular reabsorption has been observed at doses between 7.5 mg and 30 mg.

Specific Populations

Pediatric Patients

In pediatric patients receiving methotrexate for acute lymphoblastic leukemia (6.3 mg/m² to 30

mg/m²), the terminal half-life has been reported to range from 0.7 to 5.8 hours [see *Use in Specific Populations* (8.4)].

Patients with Renal impairment

The elimination half-life of methotrexate increases with the severity of renal impairment, with high inter-individual variability [see *Use in Specific Populations* (8.6)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Methotrexate has been evaluated in a number of animal studies for carcinogenic potential with inconclusive results. There is evidence that methotrexate causes chromosomal damage to animal somatic cells and human bone marrow cells [see *Use in Specific Populations* (8.1, 8.2, 8.3)].

15 REFERENCES

1. “OSHA Hazardous Drugs.” OSHA. <http://www.osha.gov/SLTC/hazardousdrugs/index.html>.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Methotrexate Injection is a clear orange-yellow, isotonic, sterile, preservative-free solution supplied in a carton containing 1 single-dose vial.

- 5 grams/50 mL (100 mg/mL) NDC 16729-516-11

Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

PROTECT FROM LIGHT.

Methotrexate Injection is a hazardous drug. Follow applicable special handling and disposal procedures.¹

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Embryo-Fetal Toxicity

- Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy [see *Contraindications* (4), *Warnings and Precautions* (5.1), and *Use in Specific Populations* (8.1)].
- Advise females of reproductive potential to use effective contraception during methotrexate therapy and for 6 months after the final dose [see *Warnings and Precautions* (5.1) and *Use in Specific Populations* (8.3)].
- Advise males of reproductive potential to use effective contraception during methotrexate therapy and for 3 months after the final dose [see *Warnings and Precautions* (5.1) and *Use in Specific Populations* (8.3)].

Hypersensitivity Reactions

Advise patients of the potential risk of hypersensitivity and that Methotrexate Injection is contraindicated in patients with a history of severe hypersensitivity to methotrexate. Advise patients to seek immediate medical attention if signs or symptoms of a hypersensitivity reaction occur [*see Warnings and Precautions (5.2)*].

Myelosuppression and Serious Infections

Advise patient to contact their healthcare provider immediately for new onset fever, symptoms of infection, easy bruising or persistent bleeding [*see Warnings and Precautions (5.3, 5.4)*].

Renal Toxicity

Advise patients that methotrexate can cause renal toxicity. Advise patients to immediately contact their healthcare provider for signs or symptoms of renal toxicity, such as marked increases or decreases in urinary output [*see Warnings and Precautions (5.5)*].

Hepatotoxicity

Advise patients to report signs or symptoms of hepatic toxicity and avoidance of alcohol during methotrexate treatment [*see Warnings and Precautions (5.6)*].

Neurotoxicity

Advise patient to contact their healthcare provider immediately if they develop new neurological symptoms [*see Warnings and Precautions (5.7)*].

Gastrointestinal Toxicity

Advise patients to contact their healthcare provider if they develop diarrhea, vomiting, or stomatitis. Advise patients to immediately contact their healthcare provider for high fever, rigors, persistent or severe abdominal pain, severe constipation, hematemesis, or melena [*see Warnings and Precautions (5.8)*].

Pulmonary Toxicity

Advise patients to contact their healthcare provider for symptoms of cough, fever, and dyspnea [*see Warnings and Precautions (5.9)*].

Dermatologic Toxicity

Advise patients that Methotrexate Injection can cause serious skin rash and to immediately contact their healthcare provider for new or worsening skin rash. Advise patients to avoid excessive sun exposure and to use sun protection measures [*see Warnings and Precautions (5.10)*].

Secondary Malignancies

Advise patients on the risk of second primary malignancies during treatment with Methotrexate Injection [*see Warnings and Precautions (5.12)*].

Lactation

Advise women not to breastfeed during treatment with methotrexate and for 1 week after the final dose [*see Use in Specific Populations (8.2)*].

Infertility

Advise females and males of reproductive potential that methotrexate may cause impairment of fertility [see *Use in Specific Populations (8.3)*].

Drug Interactions

- Advise patients and caregivers to inform their healthcare provider of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products [see *Drug Interactions (7)*].
- Instruct patients to not take products containing folic acid or folinic acid unless directed to do so by their healthcare provider [see *Warnings and Precautions (5.11)*].

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Manufactured By:

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Patient Information
METHOTREXATE (Meth-oh-trex-ate)
Injection
for intravenous use

What is the most important information I should know about Methotrexate Injection?

Methotrexate Injection can cause serious side effects that may be severe and lead to death, including: Harm to an unborn baby, including birth defects or death of an unborn baby.

Females who can become pregnant:

- Your healthcare provider should do a pregnancy test before you start taking Methotrexate Injection to see if you are pregnant.
- You and your healthcare provider will decide if you will receive Methotrexate Injection to treat your cancer if you are pregnant.
- Use effective birth control (contraception) during treatment and for **6** months after your final dose of Methotrexate Injection. Ask your healthcare provider what forms of birth control you can use during this time.

Tell your healthcare provider right away if you become pregnant or think you are pregnant during treatment with Methotrexate Injection.

Males with female partners who are able to become pregnant:

- Use effective birth control during treatment and for **3** months after your final dose of Methotrexate Injection.
Tell your healthcare provider right away if your female partner becomes pregnant during treatment with Methotrexate Injection.

Severe allergic reactions. Severe allergic reactions can happen with Methotrexate Injection.

- **Do not receive Methotrexate Injection** if you have had a severe allergic reaction to methotrexate in the past.
Get medical help right away if you develop any of the signs or symptoms of a severe allergic reaction to Methotrexate Injection, including:
 - skin rash, itching, and hives
 - swelling of the face, lips, tongue, or throat, or trouble swallowing
 - dizziness or lightheadedness
 - trouble breathing
 - wheezing
 - throat tightness
 - runny or stuffy nose
 - fast heart rate
 - chest pain
 - feeling faint

Decreased blood cell counts. Methotrexate Injection can affect your bone marrow and cause decreased red blood cell counts, white blood cell counts, and platelet counts, and a condition where your bone marrow cannot produce these blood cells (aplastic anemia). These decreased blood cell counts can be severe and may lead to a serious infection, the need for blood transfusions, treatment in a hospital, and can be life-threatening. Your healthcare provider will check your blood cell counts before you start and during treatment with Methotrexate Injection. Your healthcare provider will watch you closely for infections during treatment with Methotrexate Injection.

Call your healthcare provider right away if you develop:

- a new fever (temperature of 100.4°F or higher)
- symptoms of infection
- easy bruising or bleeding that will not stop

Your healthcare provider may give you medicines to support your blood counts or give you transfusions if needed, and change your dose or stop your treatment with Methotrexate Injection if needed.

Serious infections. People who receive treatment with Methotrexate Injection have an increased risk of developing serious infections that can be life-threatening or lead to death. These infections include:

- bacterial infections
- fungal infections
- viral infections
- certain infections that happen because your immune system is weakened
- hepatitis B infection that comes back (reactivation)
- tuberculosis (TB) infection that is new or that comes back (reactivation)
- shingles (herpes zoster)
- cytomegalovirus infections

Your healthcare provider will closely watch you for signs and symptoms of infection during treatment with Methotrexate Injection. Your healthcare provider may hold or stop your treatment with Methotrexate Injection if you develop a serious infection.

Kidney problems. Methotrexate Injection can cause kidney damage including sudden kidney failure that may not go away (irreversible). People who already have kidney problems have an increased risk of kidney problems with Methotrexate Injection. Your healthcare provider will check your kidney function during treatment and will hold or stop Methotrexate Injection treatment as needed for severe kidney damage.

Call your healthcare provider right away if you have signs or symptoms of kidney problems such as a big change in the amount of urine that you make, either increased or decreased.

Liver problems. Methotrexate Injection can cause severe liver problems including liver scarring (fibrosis), cirrhosis, and liver failure that may not get better (possibly irreversible) and can cause death.

- Your healthcare provider will do tests to monitor your liver function before you start and during treatment with Methotrexate Injection, and may hold or stop your treatment with Methotrexate Injection, if needed.
- **The risk of liver problems is increased with heavy use of alcohol. Avoid drinking alcohol during Methotrexate Injection treatment.**

Tell your healthcare provider if you develop any signs or symptoms of liver problems during treatment with Methotrexate Injection, including:

- | | |
|-------------------------------|---|
| ○ tiredness | ○ swelling in your legs, feet, or ankles |
| ○ easy bleeding or bruising | ○ weight loss |
| ○ loss of appetite | ○ itchy skin |
| ○ nausea | ○ yellowing of your skin or the white part of your eyes |
| ○ difficulty thinking clearly | ○ weakness |

Brain and spinal cord (nervous system) problems. Methotrexate Injection can cause nervous system problems that can be severe and last for a short time or last for a long time. These nervous system problems can get progressively worse, may not get better (possibly irreversible), and can cause death.

- Serious nervous system problems can happen in children who receive Methotrexate Injection, including seizures that can begin on one side of the brain (focal seizures) or on both sides of the brain (generalized seizures).
- The risk for a nervous system problem called leukoencephalopathy is increased in people who have had radiation treatment to their head and spine (craniospinal irradiation) in the past. Call your healthcare provider if you develop any new neurological symptoms.
- People who receive high-dose Methotrexate Injection can develop sudden symptoms that are like the symptoms of a stroke, but they last a short time and may go away (transient).

Call your healthcare provider right away if you or your child develop any new signs or symptoms of a nervous system problem during treatment with Methotrexate Injection, including:

- | | |
|-------------------------------------|--------------|
| ○ confusion | ○ coma |
| ○ weakness on one side of your body | ○ headache |
| ○ sudden blindness that goes away | ○ back pain |
| ○ seizures | ○ stiff neck |
| | ○ fever |

Severe stomach and intestine (gastrointestinal) problems.

Methotrexate Injection can cause diarrhea, vomiting, mouth sores, stomach and intestinal inflammation with severe bleeding, and tears in the intestinal wall (perforation), and can lead to death.

- People who have stomach ulcers (peptic ulcer disease) or ulcerative colitis (UC) have a higher risk of developing severe stomach and intestine problems with Methotrexate Injection.
- Your healthcare provider may hold or stop your treatment with Methotrexate Injection if any of these severe stomach and intestinal problems happen, and treat you as needed.
- Call your healthcare provider if you develop diarrhea, vomiting, inflammation or sores in your mouth.

Call your healthcare provider right away if you develop:

- | | |
|--|-----------------------------|
| ○ high fever | ○ severe constipation |
| ○ shaking chills | ○ if you are vomiting blood |
| ○ stomach-area (abdomen) pain that is severe or does not go away | ○ blood in your stools |

Lung problems. Lung problems can happen suddenly (acute) with Methotrexate Injection or they can develop over a long period-of-time (chronic). Lung problems may not get better (possibly irreversible) and can cause death in anyone taking Methotrexate Injection. Your healthcare provider will monitor you for lung problems during treatment with Methotrexate Injection. Your healthcare provider may hold or stop your treatment with Methotrexate Injection, if needed.

Call your healthcare provider if you develop symptoms of a lung problem including: cough, fever, and trouble breathing.

Skin reactions. Severe skin reactions can happen with Methotrexate Injection, that can be serious and can lead to death.

• **In people with psoriasis:** Your psoriasis may get worse if you are exposed to sunlight or other types of ultraviolet light.

• Methotrexate Injection can cause reactivation of skin reactions that can happen after radiation therapy (radiation

recall) and can cause sunburn to come back (photodermatitis).

Limit sunlight exposure during treatment with Methotrexate Injection. Use sunscreen and wear protective clothing when you will be exposed to sunlight during treatment with Methotrexate Injection.

Call your healthcare provider right away if you develop a new or worsening skin rash during treatment with Methotrexate Injection.

See “**What are the possible side effects of Methotrexate Injection?**” for more information about side effects.

What is Methotrexate Injection?

Methotrexate Injection is a prescription medicine used in adults and children:

- in combination with other chemotherapy medicines to treat acute lymphoblastic leukemia (ALL)
- to treat non-Hodgkin lymphoma
- in combination with other chemotherapy medicines to treat osteosarcoma

Do not receive Methotrexate Injection if you:

- have had a severe allergic reaction to Methotrexate Injection. See “**What is the most important information I should know about Methotrexate Injection?**”

Before you receive Methotrexate Injection, tell your healthcare provider about all of your medical conditions, including if you:

- have kidney problems or are receiving dialysis treatments
- have liver problems
- have a history of neurologic problems, including seizures
- drink-alcohol containing beverages during treatment with Methotrexate Injection, or if there are any changes in the amount of alcoholic beverages you drink
- have fluid in your stomach-area (ascites)
- have lung problems or fluid in your lungs (pleural effusion)
- plan to have any surgeries with general anesthesia, including dental surgery
- have stomach ulcers (peptic ulcer disease)
- have ulcerative colitis
- have recently received or are scheduled to receive a vaccine. You should not receive live vaccines during treatment with Methotrexate Injection.
- are breastfeeding or plan to breastfeed. Methotrexate may pass into your breast milk. Do not breastfeed during treatment and for 1 week after your last dose of Methotrexate Injection.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Taking certain medicines can affect the amount of methotrexate in your blood and can increase your risk for serious side effects.

How will I receive or take Methotrexate Injection?

- You will receive Methotrexate Injection through an intravenous (IV) line in your vein by your healthcare provider.
- Your healthcare provider will decide your dose and how often you need to receive it, depending on your medical condition that is being treated.
- If you are receiving high-dose Methotrexate Injection to treat your cancer, you will receive the medicine leucovorin to help prevent severe side effects (“rescue”) to your bone marrow and other normal cells in your body. You will also receive intravenous (IV) fluids and other medicines to help prevent and treat side effects.
- If you are receiving a “moderate-dose” of Methotrexate Injection to treat your cancer, you may also receive leucovorin.
- **Do not take folic acid or folinic acid during treatment with Methotrexate Injection to treat your cancer,** unless your healthcare provider tells you to. Taking folic acid or folinic acid with Methotrexate Injection may make your treatment less effective.
- Your healthcare provider will do blood tests to check for side effects during treatment with Methotrexate Injection.
- Your healthcare provider may stop your treatment, change when you receive your treatment, or change the dose of your treatment if you have certain side effects while receiving Methotrexate Injection.
- If you miss receiving a dose of Methotrexate Injection, call your healthcare provider for instructions about when to receive your next dose of Methotrexate Injection.

What are the possible side effects of Methotrexate Injection? Methotrexate Injection can cause serious side effects, including:

- See “**What is the most important information I should know about Methotrexate Injection?**”
- **New (secondary) cancers.** New (secondary) cancers can happen in people who take or receive Methotrexate Injection at any dose.

- Certain blood cancers can happen during treatment with Methotrexate Injection. In some cases, these blood cancers may totally go away (regress completely) after Methotrexate Injection is stopped.
- If you develop one of these blood cancers during treatment with Methotrexate Injection, your healthcare provider will stop your treatment, and treat as needed if the new cancer does not go away after Methotrexate Injection is stopped.
- **Tumor lysis syndrome (TLS).** TLS is caused by the fast breakdown of cancer cells. TLS can cause kidney failure and the need for dialysis treatment, abnormal heart rhythm, seizure, and sometimes death. Your healthcare provider may do blood tests to check you for TLS during your treatment with Methotrexate Injection. Your healthcare provider will treat you as needed to prevent or manage TLS if you develop it during treatment with Methotrexate Injection.
- **Increased risk of soft tissue and bone problems due to receiving Methotrexate Injection in combination with radiation therapy.** In people who receive Methotrexate Injection, some soft tissue in your body may die and some bone cells may die. People who receive radiation therapy in combination with Methotrexate Injection have an increased risk of this happening.

The most common side effects of Methotrexate Injection include:

- mouth sores or ulcers
- decreased white blood cell count. See “**What is the most important information I should know about Methotrexate Injection?**”
- nausea
- upset stomach

Possible fertility problems (infertility) in males and females. Methotrexate Injection can cause fertility problems in males and females, and cause sperm production to stop in males, and menstrual problems in females. In females, your periods (menstrual cycle) may be irregular or completely stop when you receive Methotrexate Injection. Your periods may or may not return to normal following treatment. It is not known if your fertility will return after treatment. Talk to your healthcare provider about your risk for infertility if this is a concern for you.

These are not all of the possible side effects of Methotrexate Injection.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of Methotrexate Injection.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet.

You can ask your pharmacist or healthcare provider for information about Methotrexate Injection that is written for health professionals.

What are the ingredients in Methotrexate Injection?

Active ingredient: methotrexate.

Inactive ingredients of Methotrexate Injection Preservative-free: May contain sodium hydroxide to adjust pH to 8.5.

Manufactured For: Accord Healthcare, Inc., 1009, Slater Road, Suite 210-B, Durham, NC 27703, USA.

Manufactured By: Intas Pharmaceuticals Limited, Plot No. 5 to 14, Pharmez, Nr. Village Matoda, Bavla Road, Ta.-Sanand, Dist. Ahmedabad-382 213, India.

For more information, call 1-866-941-7875