HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use XATMEP® safely and effectively. See full prescribing information for XATMEP.

XATMEP (methotrexate) oral solution
Initial U.S. Approval: 1953

WARNING: SEVERE TOXIC REACTIONS, INCLUDING EMBRYO-FETAL TOXICITY, AND RISK OF MEDICATION ERRORS
See full prescribing information for complete boxed warning.

- **Methotrexate can cause severe or fatal toxicities. Monitor closely and modify dose or discontinue for the following toxicities: bone marrow suppression (5.1), infection (5.2), renal (5.3), gastrointestinal (5.4), hepatic (5.5), pulmonary (5.6), hypersensitivity and dermatologic (5.7).**
- **Methotrexate can cause embryo-fetal toxicity and fetal death. Use in polyarticular juvenile idiopathic arthritis is contraindicated in pregnancy (4). Consider the benefits and risks of XATMEP and risks to the fetus when prescribing XATMEP to a pregnant patient with a neoplastic disease. Advise patients to use effective contraception during and after treatment with XATMEP (5.9, 8.1, 8.3).**
- **Oral methotrexate when inadvertently administered once daily has resulted in death *[see Warnings and Precautions (5.15)]*.**

----------RECENT MAJOR CHANGES----------

Boxed Warning	05/2026
Warnings and Precautions (5.15)	05/2026

----------INDICATIONS AND USAGE----------

XATMEP is a folate analog metabolic inhibitor indicated for the:

- Treatment of pediatric patients with acute lymphoblastic leukemia (ALL) as a component of a combination chemotherapy maintenance regimen (1.1).
- Management of pediatric patients with active polyarticular juvenile idiopathic arthritis (pJIA) who are intolerant of or had an inadequate response to first-line therapy (1.2).

----------DOSAGE AND ADMINISTRATION----------

- Use another formulation of methotrexate for patients requiring dosing via routes of administration other than oral (2.1).
- Measure with an accurate measuring device (2.1).

Recommended Dosage:

- ALL: 20 mg/m^2 one time weekly (2.2).
- pJIA: Starting dose of 10 mg/m^2 one time weekly (2.3).

----------DOSAGE FORMS AND STRENGTHS----------

Oral solution: 2.5 mg/mL (3).

----------CONTRAINDICATIONS----------

- Pregnancy (patients with pJIA) (4).
- Severe hypersensitivity to methotrexate (4).

----------WARNINGS AND PRECAUTIONS----------

- Secondary malignancies can occur. In case of immunosuppression-associated lymphoma, discontinue methotrexate before starting treatment for lymphoma (5.8).
- Immunizations may be ineffective (5.10).
- Effects on reproduction: May cause impairment of fertility, oligospermia and menstrual dysfunction (5.11, 8.3).

----------ADVERSE REACTIONS----------

Most common adverse reactions are: ulcerative stomatitis, leukopenia, nausea, abdominal distress, and elevated liver function tests. Other frequently reported adverse reactions are malaise, fatigue, chills and fever, dizziness and decreased resistance to infection (6).

To report SUSPECTED ADVERSE REACTIONS, contact Azurity Pharmaceuticals, Inc., at 1-800-461-7449 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

- Oral Antibiotics: May increase hematologic and gastrointestinal toxicity. Monitor patients accordingly (7.1).
- Nitrous Oxide: May increase the risk of toxicity (7.1).
- NSAIDs, Aspirin, and Steroids: May elevate and prolong serum methotrexate levels and increase gastrointestinal toxicity. Monitor patients accordingly (7.1).

----------USE IN SPECIFIC POPULATIONS----------

Lactation: Advise women not to breastfeed (8.2).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 05/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SEVERE TOXIC REACTIONS, INCLUDING EMBRYO-FETAL TOXICITY, AND RISK OF MEDICATION ERRORS

- **Methotrexate can cause the following severe or fatal adverse reactions. Monitor closely and modify dose or discontinue methotrexate as appropriate.**
  - **Bone marrow suppression *[see Warnings and Precautions (5.1)]***
  - **Serious infections *[see Warnings and Precautions (5.2)]***
  - **Renal toxicity and increased toxicity with renal impairment *[see Warnings and Precautions (5.3)]***
  - **Gastrointestinal toxicity *[see Warnings and Precautions (5.4)]***
  - **Hepatic toxicity *[see Warnings and Precautions (5.5)]***
  - **Pulmonary toxicity *[see Warnings and Precautions (5.6)]***
  - **Hypersensitivity and dermatologic reactions *[see Warnings and Precautions (5.7)]***
- **Methotrexate can cause embryo-fetal toxicity, including fetal death. Use in pJIA is contraindicated in pregnancy. Consider the benefits and risks of XATMEP and risks to the fetus when prescribing XATMEP to a pregnant patient with a neoplastic disease. Advise females and males of reproductive potential to use effective contraception during and after treatment with XATMEP *[see Contraindications (4), Warnings and Precautions (5.9), Use in Specific Populations (8.1, 8.3)].***
- **Oral methotrexate when inadvertently administered once daily has resulted in death *[see Warnings and Precautions (5.15)]*.**

1 INDICATIONS AND USAGE

1.1 Acute Lymphoblastic Leukemia

XATMEP is indicated for the treatment of pediatric patients with acute lymphoblastic leukemia (ALL) as part of a multi-phase, combination chemotherapy maintenance regimen.

1.2 Polyarticular Juvenile Idiopathic Arthritis

XATMEP is indicated in the management of pediatric patients with active polyarticular juvenile idiopathic arthritis (pJIA) who have had an insufficient therapeutic response to, or are intolerant of, an adequate trial of first-line therapy including full dose non-steroidal anti-inflammatory agents (NSAIDs).

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Information

XATMEP is intended for oral use only. Use another formulation of methotrexate for alternative dosing in patients who require dosing via other routes of administration. Instruct patients and caregivers that the recommended dose should be taken weekly, as directed, and that mistaken daily use of the recommended dose has led to fatal toxicity *[see Warnings and Precautions (5.15), Overdosage (10)]*.

It is important that XATMEP be measured with an accurate measuring device *[see Warnings and Precautions (5.15), Patient Counseling Information (17)]*. A household teaspoon is not an accurate

measuring device. A pharmacist can provide an appropriate device and can provide instructions for measuring the correct dose.

2.2 Acute Lymphoblastic Leukemia

The recommended starting dose of XATMEP, in multi-agent combination chemotherapy maintenance regimens, is 20 mg/m^2 given one time weekly. After initiating XATMEP, continuation of appropriate dosing requires periodic monitoring of absolute neutrophil count (ANC) and platelet count to assure sufficient drug exposure (that is to maintain ANC at a desirable level) and to adjust for excessive hematological toxicity.

2.3 Polyarticular Juvenile Idiopathic Arthritis

The recommended starting dose of XATMEP is 10 mg/m^2 given one time weekly.

Dosages should be tailored to the individual patient and adjusted gradually to achieve an optimal response. Although there is experience with doses up to 30 mg/m^2/week in pediatric patients, doses greater than 20 mg/m^2/week may result in a significant increase in the incidence and severity of serious toxic reactions, especially bone marrow suppression. Doses between 20 and 30 mg/m^2/week (0.65 to 1 mg/kg/week) may have better absorption and fewer gastrointestinal side effects if methotrexate is administered by an alternative route using another formulation.

Therapeutic response usually begins within 3 to 6 weeks and the patient may continue to improve for another 12 weeks or more.

Certain side effects such as mouth sores may be reduced by folate supplementation with methotrexate in pJIA.

2.4 Evaluations Prior to Starting Methotrexate

Assess hematologic, hepatic, and renal function before beginning, as well as periodically during and before reinstituting, therapy with XATMEP *[see Warnings and Precautions (5.1, 5.3, 5.5, 5.7, 5.14)]*. Exclude pregnancy in females of reproductive potential before starting XATMEP *[see Contraindications (4), Warnings and Precautions (5.9), Use in Specific Populations (8.1, 8.3)]*.

2.5 Handling Information

XATMEP is a cytotoxic drug. Follow applicable special handling and disposal procedures.[1]

3 DOSAGE FORMS AND STRENGTHS

XATMEP is a clear yellow to orange oral solution that contains 2.5 mg of methotrexate per milliliter.

4 CONTRAINDICATIONS

XATMEP is contraindicated in the following:

- Pregnancy in patients with non-malignant diseases. XATMEP can cause embryo-fetal toxicity and fetal death when administered during pregnancy *[see Warnings and Precautions (5.9), Use in Specific Populations (8.1)]*.
- Patients with severe hypersensitivity to methotrexate *[see Warnings and Precautions (5.7), Adverse Reactions (6.1, 6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Bone Marrow Suppression

XATMEP suppresses hematopoiesis and can cause severe and life-threatening pancytopenia, anemia, leukopenia, neutropenia, and thrombocytopenia.

Obtain blood counts at baseline and periodically during treatment. Monitor patients for possible clinical complications of bone marrow suppression. Provide supportive care and modify dose or discontinue XATMEP as needed.

5.2 Serious Infections

Patients treated with XATMEP 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 infections.

Monitor patients for the signs and symptoms of infection during and after treatment with XATMEP and treat promptly. Consider dose modification or discontinuation of XATMEP in patients who develop serious infections *[see Warnings and Precautions (5.1)].*

5.3 Renal Toxicity and Increased Toxicity with Renal Impairment

XATMEP can cause renal damage including acute renal failure. Monitor renal function to decrease the risk of renal injury and mitigate renal toxicity.

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

5.4 Gastrointestinal Toxicity

XATMEP can cause diarrhea, vomiting, stomatitis, hemorrhagic enteritis, and fatal intestinal perforation. Patients with peptic ulcer disease or ulcerative colitis are at a greater risk of developing severe gastrointestinal adverse reactions.

Interrupt or discontinue XATMEP and institute appropriate supportive care as needed.

Unexpectedly severe and fatal gastrointestinal toxicity can occur with concomitant administration of XATMEP (primarily at high dosage) and nonsteroidal anti-inflammatory drugs (NSAIDs) *[see Drug Interactions (7.1)]*.

5.5 Hepatic Toxicity

XATMEP can cause severe and potentially irreversible hepatotoxicity including fibrosis, cirrhosis, and fatal liver failure. Avoid use of XATMEP in patients with chronic liver disease.

Assess liver function prior to initiating XATMEP and monitor liver function tests during treatment. Interrupt or discontinue XATMEP as appropriate. Transient asymptomatic acute liver enzyme elevations are common and are not predictive of subsequent hepatic disease. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis.

Other risk factors for hepatotoxicity include alcoholism, obesity, diabetes, hyperlipidemia, previous significant exposure to liver toxins, history of liver disease, family history of inheritable liver disease, persistent abnormal liver chemistry findings, duration of therapy, and advanced age.

5.6 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 interrupt or discontinue XATMEP as appropriate.

5.7 Hypersensitivity and Dermatologic Reactions

Severe, including fatal, dermatologic reactions, such as toxic epidermal necrolysis, Stevens-Johnson syndrome, exfoliative dermatitis, skin necrosis, erythema multiforme, can occur with methotrexate. Discontinue XATMEP if severe dermatologic reactions occur.

Anaphylaxis can occur with methotrexate. If anaphylaxis or any other serious hypersensitivity reaction occurs, immediately discontinue methotrexate and institute appropriate therapy. Methotrexate is contraindicated for use in patients with a history of severe hypersensitivity.

Radiation dermatitis and sunburn may be “recalled” by the use of methotrexate.

5.8 Secondary Malignancies

Secondary malignancies can occur at all dose levels of methotrexate.

There have been instances of lymphoproliferative disease associated with low-dose oral methotrexate which have regressed completely following withdrawal of methotrexate without institution of antineoplastic therapy. Discontinue XATMEP first and institute appropriate treatment if the lymphoma does not regress.

5.9 Embryo-Fetal Toxicity

Based on published reports and methotrexate’s mechanism of action, methotrexate can cause embryo-fetal toxicity and fetal death when administered to a pregnant woman. In pregnant women with non-malignant diseases, methotrexate is contraindicated. Consider the benefits and risks of XATMEP and risks to the fetus when prescribing XATMEP to a pregnant patient with a neoplastic disease. Advise females of reproductive potential to use effective contraception during therapy and for 6 months after the final dose. Advise males of reproductive potential to use effective contraception during and for at least 3 months after the final methotrexate dose *[see Contraindications (4), Use in Specific Populations (8.1, 8.3), Clinical Pharmacology (12.1)].*

5.10 Ineffective Immunization and Risks Associated with Live Vaccines

Immunization may be ineffective when given during XATMEP therapy.

Immunization with live virus vaccines is not recommended. There have been reports of disseminated vaccinia infections after smallpox immunization in patients receiving methotrexate therapy.

5.11 Effects on Reproduction

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

5.12 Increased Toxicity 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 administration *[see Clinical Pharmacology (12.3)]*.

5.13 Soft Tissue and Bone Toxicity with Radiation Therapy

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

5.14 Laboratory Tests

Closely monitor patients undergoing XATMEP therapy so that toxic effects are detected promptly. In general, monitoring of the following parameters is recommended: hematology at least monthly, renal function and liver function every 1 to 2 months *[see Warnings and Precautions (5.1, 5.3, 5.5)]*.

Increase monitoring frequency during initial dosing, dose changes, or during periods of increased risk of elevated methotrexate blood levels (e.g., dehydration).

Liver Function Tests

Transient liver function test abnormalities are observed frequently after methotrexate administration and are usually not cause for modification of methotrexate therapy. Persistent liver function test abnormalities, and/or depression of serum albumin may be indicators of serious liver toxicity and require evaluation *[see Warnings and Precautions (5.5)]*.

Pulmonary Function Tests

Pulmonary function tests may be useful if methotrexate-induced lung disease is suspected, especially if baseline measurements are available *[see Warnings and Precautions (5.6)]*.

5.15 Risk of Serious Adverse Reactions with Medication Error

Both the physician and pharmacist should emphasize to the patient that the recommended dose is taken one time weekly, as directed, and that mistaken daily use of the recommended dose has led to fatal toxicity *[see Dosage and Administration (2.1), Overdosage (10)]*.

Advise patients to measure XATMEP with an accurate milliliter measuring device. Inform patients that a household teaspoon is not an accurate measuring device and could lead to overdosage, which can result in serious adverse reactions *[see Overdosage (10)]*. Advise patients to ask their pharmacist to recommend an appropriate measuring device and for instructions for measuring the correct dose *[see Dosage and Administration (2.1), Patient Counseling Information (17)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling.

- Bone Marrow Suppression *[see Warnings and Precautions (5.1)]*
- Serious Infections *[see Warnings and Precautions (5.2)]*
- Renal Toxicity and Increased Toxicity with Renal Impairment *[see Warnings and Precautions (5.3)]*
- Gastrointestinal Toxicity *[see Warnings and Precautions (5.4)]*

- Hepatic Toxicity *[see Warnings and Precautions (5.5)]*
- Pulmonary Toxicity *[see Warnings and Precautions (5.6)]*
- Hypersensitivity and Dermatologic Reactions *[see Warnings and Precautions (5.7)]*
- Secondary Malignancies *[see Warnings and Precautions (5.8)]*
- Ineffective Immunization and Risks Associated with Live Vaccines *[see Warnings and Precautions (5.10)]*
- Infertility *[see Warnings and Precautions (5.11)]*
- Increased Toxicity Due to Third-Space Accumulation [*see Warnings and Precautions (5.12)]*
- Soft Tissue and Bone Toxicity with Radiation Therapy *[see Warnings and Precautions (5.13)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug, and may not reflect the rates observed in practice.

The most frequently reported adverse reactions include ulcerative stomatitis, leukopenia, nausea, and abdominal distress. Other frequently reported adverse reactions are malaise, fatigue, chills, fever, dizziness, and decreased resistance to infection. Folate deficiency states may increase methotrexate toxicity.

Polyarticular Juvenile Idiopathic Arthritis

The approximate incidences of adverse reactions reported in pediatric patients with JIA treated with oral, weekly doses of methotrexate (5 to 20 mg/m^2/week or 0.1 to 0.65 mg/kg/week) were as follows (virtually all patients were receiving concomitant nonsteroidal anti-inflammatory drugs, and some also were taking low doses of corticosteroids): elevated liver function tests, 14%; gastrointestinal reactions (e.g., nausea, vomiting, diarrhea), 11%; stomatitis, 2%; leukopenia, 2%; headache, 1.2%; alopecia, 0.5%; dizziness, 0.2%; and rash, 0.2%. Although there is experience with dosing up to 30 mg/m^2/week in JIA, the published data for doses above 20 mg/m^2/week are too limited to provide reliable estimates of adverse reaction rates.

6.2 Postmarketing Experience

Additional adverse reactions which have been identified during postmarketing use of methotrexate are listed below by organ system.

Blood and Lymphatic System Disorders: Suppressed hematopoiesis causing anemia, aplastic anemia, pancytopenia, leukopenia, neutropenia, thrombocytopenia, lymphadenopathy, lymphoproliferative disorders (including reversible), hypogammaglobulinemia

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

Eye Disorders: Optic neuropathy, transient blindness, blurred vision, ocular irritation, conjunctivitis, xerophthalmia

Gastrointestinal Disorders: Gingivitis, pharyngitis, stomatitis, anorexia, nausea, vomiting, diarrhea, hematemesis, melena, gastrointestinal ulceration and bleeding, enteritis, pancreatitis

Hepatobiliary Disorders: Hepatotoxicity, acute hepatitis, chronic fibrosis and cirrhosis, decreased serum albumin, liver enzyme elevations

Immune System Disorders: Vasculitis, lymphomas, and anaphylactoid reactions

Infections: Fatal opportunistic infections (most commonly *Pneumocystis jiroveci* pneumonia). There have also been reports of other infections, pneumonia, sepsis, nocardiosis, histoplasmosis, cryptococcosis, *Herpes zoster*, *Herpes simplex* hepatitis, and disseminated *Herpes simplex*.

Metabolism: Hyperglycemia and tumor lysis syndrome

Musculoskeletal System: Stress fracture, soft tissue necrosis, osteonecrosis, arthralgia, myalgia, osteoporosis

Nervous System Disorders: Headaches, drowsiness, blurred vision, transient blindness, speech impairment (including dysarthria and aphasia), hemiparesis, paresis and convulsions have also occurred following administration of methotrexate.

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

Renal Disorders: Azotemia, hematuria, proteinuria, cystitis

Reproductive Disorders: Defective oogenesis or spermatogenesis, menstrual dysfunction, loss of libido, impotence, vaginal discharge, gynecomastia

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

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

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on XATMEP

Oral Antibiotics

Penicillins may reduce the renal clearance of methotrexate; increased serum concentrations of methotrexate with concomitant hematologic and gastrointestinal toxicity have been observed with methotrexate. Monitor patients accordingly *[see Warnings and Precautions (5.1, 5.4)]*.

Trimethoprim/sulfamethoxazole has been reported to increase bone marrow suppression in patients receiving methotrexate. Monitor patients accordingly *[see Warnings and Precautions (5.1)]*.

Hepatotoxins

The potential for increased hepatotoxicity when methotrexate is administered with other hepatotoxic agents has not been evaluated; however, hepatotoxicity has been reported in such cases. Monitor patients receiving XATMEP with other potential hepatotoxins (e.g., azathioprine, retinoids, and sulfasalazine) for possible signs of hepatotoxicity.

Probenecid

Probenecid may reduce renal elimination of methotrexate. Consider alternative drugs.

Nitrous Oxide

The use of nitrous oxide anesthesia potentiates the effect of methotrexate on folate-dependent metabolic pathways, resulting in the potential for increase toxicity. Avoid the simultaneous use of nitrous oxide and methotrexate.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), Aspirin, and Steroids

Concomitant administration of some NSAIDs with high dose methotrexate therapy has been reported to elevate and prolong serum methotrexate levels, resulting in deaths from severe hematologic and gastrointestinal toxicity.

Caution should be used when NSAIDs and salicylates are administered concomitantly with lower doses of methotrexate, including XATMEP. These drugs have been reported to reduce the tubular secretion of methotrexate in an animal model and may enhance its toxicity.

Despite the potential interactions, studies of methotrexate in patients with rheumatoid arthritis, including patients with polyarticular juvenile idiopathic arthritis (pJIA), have usually included concurrent use of constant dosage regimens of NSAIDs, without apparent problems. It should be appreciated, however, that the doses used in pJIA (10 mg/m^2/week as starting dose) are somewhat lower than those used in acute lymphoblastic leukemia and that larger doses could lead to unexpected toxicity. Aspirin, NSAIDs, and/or low dose steroids may be continued, although the possibility of increased toxicity with concomitant use of NSAIDs including salicylates has not been fully explored. Steroids may be reduced gradually in patients who respond to methotrexate.

7.2 Effect of XATMEP on Other Drugs

Theophylline

Methotrexate may decrease the clearance of theophylline. Monitor theophylline levels when coadministered with XATMEP.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on published reports and methotrexate's mechanism of action, methotrexate is a teratogen that can cause embryo-fetal toxicity and fetal death when administered to a pregnant woman *[see Data and Clinical Pharmacology (12.1)]*. In pregnant women with non-malignant disease, XATMEP is contraindicated. Consider the benefits and risks of XATMEP and risks to the fetus when prescribing XATMEP to a pregnant patient with a neoplastic disease. There are no animal data that meet current standards for nonclinical developmental toxicity studies.

The estimated background risk of major birth defects and miscarriage for the indicated populations are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Human Data

Published data from cases, 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 by U.S. and European teratology information services evaluated pregnancy outcomes in women taking methotrexate less than or equal to 30 mg/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 autoimmune disease comparators (22.5%, 95% CI 16.8-29.7) and unexposed nonautoimmune disease comparators (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 autoimmune disease comparators (adjusted odds ratio (OR) 1.8 [95% CI 0.6-5.7]) and nonautoimmune disease comparators (adjusted OR 3.1 [95% CI 1.03-9.5]). 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 report the presence of methotrexate in human milk in low amounts. The highest breast milk to plasma concentration ratio demonstrated was 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, including myelosuppression, from methotrexate in breastfed infants, advise women not to breastfeed during XATMEP therapy.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Test for pregnancy prior to initiating therapy with XATMEP.

Contraception

Females

XATMEP can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

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

Males

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

Infertility

Females

Based on published reports of female infertility after therapy with methotrexate, advise females of reproductive potential that XATMEP 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 of reproductive potential that XATMEP 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

Safety and effectiveness of XATMEP in pediatric patients have been established for the treatment of pediatric patients with acute lymphoblastic leukemia (ALL) as part of a multi-phase, combination chemotherapy maintenance regimen and for the management of pediatric patients with active polyarticular juvenile idiopathic arthritis (pJIA) *[see Clinical Studies (14)]*.

8.6 Renal Impairment

Methotrexate elimination is reduced in patients with impaired renal function. Monitor patients with renal impairment for an extended period of time. Consider a dose reduction or, in some cases, discontinue XATMEP administration *[see Warnings and Precautions (5.3)]*.

8.7 Hepatic Impairment

The effect of hepatic impairment on methotrexate pharmacokinetics has not been studied. Patients with hepatic impairment may be more susceptible to hepatotoxicity *[see Warnings and Precautions (5.5)]*. Consider dose adjustments or alternative treatments in patients with baseline hepatic impairment.

10 OVERDOSAGE

Manifestations

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, bone marrow suppression, mucositis, stomatitis, oral ulceration, nausea, vomiting, gastrointestinal ulceration, or gastrointestinal bleeding). In some cases, no symptoms were 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).

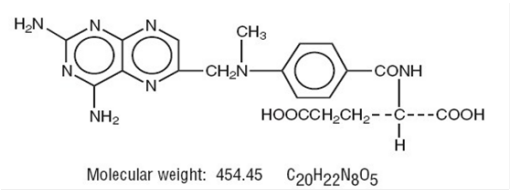
If glucarpidase is used, do not administer leucovorin within 2 hours before or after a dose of glucarpidase because leucovorin is a substrate for glucarpidase.

In cases of massive overdosage, hydration and urinary alkalinization may be necessary to prevent the precipitation of methotrexate and/or its metabolites in the renal tubules. Neither hemodialysis nor peritoneal dialysis 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

XATMEP contains methotrexate, a folate analog metabolic inhibitor.

Chemically methotrexate is N-[4-[[(2,4-diamino-6-pteridinyl)methyl]methylamino] benzoyl]-L-glutamic acid. The structural formula is:



XATMEP is a clear yellow to orange oral solution that contains 2.5 mg of methotrexate per milliliter (equivalent to 2.74 mg of methotrexate sodium/mL). Inactive ingredients include purified water, sodium citrate, citric acid, methylparaben sodium, propylparaben sodium, and sucralose. It may also contain sodium hydroxide or hydrochloric acid for pH adjustment.

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.

The mechanism of action in pJIA is unknown; it may affect immune function.

12.2 Pharmacodynamics

Two reports describe *in vitro* methotrexate inhibition of DNA precursor uptake by stimulated mono-nuclear cells, and another describes in animal polyarthritis partial correction by methotrexate of spleen cell hyporesponsiveness and suppressed IL 2 production. Other laboratories, however, have been unable to demonstrate similar effects.

12.3 Pharmacokinetics

Absorption

In pediatric patients with ALL, oral absorption of methotrexate appears to be dose dependent; the absorption of doses greater than 40 mg/m^2 is significantly less than that of lower doses. The extent of oral

absorption ranges from 23% to 95%, and the time to peak concentration (T_{max}) ranges from 0.7 hours to 4 hours after an oral dose of 15 mg/m^2.

In pediatric patients with pJIA, mean serum concentrations were 0.59 micromolar (range, 0.03 to 1.40) at 1 hour, 0.44 micromolar (range, 0.01 to 1.00) at 2 hours, and 0.29 micromolar (range 0.06 to 0.58) at 3 hours following oral administration of methotrexate at a dose of 6.4 mg/m^2/week to 11.2 mg/m^2/week.

Effect of Food

The administration of XATMEP with food did not affect the area under the curve (AUC), but decreased the maximal concentrations (C_{max}) by 50% and delayed the absorption.

Distribution

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

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

Methotrexate in serum is approximately 50% protein bound.

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

Elimination

In adults, the half-life of methotrexate following administration of low dose methotrexate (less than 30 mg/m^2) ranges from 3 hours to 10 hours.

In pediatric patients receiving methotrexate for ALL (6.3 mg/m^2 to 30 mg/m^2), the terminal half-life has been reported to range from 0.7 hours to 5.8 hours.

In pediatric patients receiving methotrexate for JIA (3.75 mg/m^2 to 26.2 mg/m^2), the terminal half-life has been reported to range from 0.9 hours to 2.3 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. A small amount of metabolism to 7-hydroxymethotrexate may occur at doses commonly prescribed. The aqueous solubility of 7-hydroxymethotrexate is 3- to 5-fold lower than the parent compound. Methotrexate is partially metabolized by intestinal flora after oral administration.

Excretion

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

Renal excretion occurs by glomerular filtration and active tubular secretion. Nonlinear elimination due to saturation of renal tubular reabsorption has been observed in patients at doses between 7.5 mg and 30 mg. Impaired renal function, as well as concurrent use of drugs such as weak organic acids that also undergo tubular secretion, can markedly increase methotrexate serum levels.

Methotrexate clearance decreases at higher doses. Delayed drug clearance has been identified as one of the major factors responsible for methotrexate toxicity. When a patient has delayed drug elimination due to compromised renal function, a third-space effusion, or other causes, methotrexate serum concentrations may remain elevated for prolonged periods.

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. Although there is evidence that methotrexate causes chromosomal damage to animal somatic cells and human bone marrow cells, the clinical significance remains uncertain.

14 CLINICAL STUDIES

Polyarticular Juvenile Idiopathic Arthritis

Clinical trials in patients with polyarticular juvenile idiopathic arthritis were performed using other formulations of methotrexate.

In a 6-month, double-blind, placebo-controlled trial of 127 pediatric patients with juvenile idiopathic arthritis (JIA) (mean age, 10.1 years; age range 2.5 to 18 years, mean duration of disease, 5.1 years) on background non-steroidal anti-inflammatory drugs (NSAIDs) and/or prednisone, methotrexate given one time weekly at an oral dose of 10 mg/m^2 provided significant clinical improvement compared to placebo as measured by either the physician's global assessment, or by a patient composite (25% reduction in the articular-severity score plus improvement in parent and physician global assessments of disease activity). Over two-thirds of the patients in this trial had polyarticular-course JIA, and the numerically greatest response was seen in this subgroup treated with 10 mg/m^2/week methotrexate. The overwhelming majority of the remaining patients had systemic-course JIA. All patients were unresponsive to NSAIDs; approximately one-third were using low dose corticosteroids. Weekly methotrexate at a dose of 5 mg/m^2 was not significantly more effective than placebo in this trial.

15 REFERENCES

"Hazardous Drugs" *OSHA*. *http://www.osha.gov/SLTC/hazardousdrugs/index.html*

16 HOW SUPPLIED/STORAGE AND HANDLING

XATMEP is a clear yellow to orange oral solution that contains 2.5 mg of methotrexate per milliliter (equivalent to 2.74 mg of methotrexate sodium/mL). It is packaged in a high-density polyethylene (HDPE) bottle with a child-resistant cap and tamper-evident seal.

XATMEP is available in bottles of 60 mL (NDC 52652-2001-6) and 120 mL (NDC 52652-2001-1).

Store XATMEP refrigerated (2°C to 8°C/36°F to 46°F) tightly closed in the original container prior to dispensing.

Once dispensed, patients may store XATMEP either refrigerated (2°C to 8°C/36°F to 46°F) or at room temperature (20°C to 25°C/68°F to 77°F) with excursions permitted to 15°C to 30°C/59°F to 86°F [see USP

Controlled Room Temperature]. If stored at room temperature, discard after 60 days. Avoid freezing and excessive heat.

17 PATIENT COUNSELING INFORMATION

Importance of Proper Dosing and Administration

Advise patients that the recommended dose should be taken *one time* weekly, as directed, and that mistaken daily use of the recommended dose has led to fatal toxicity *[see Dosage and Administration (2.1), Warnings and Precautions (5.15)]*.

Advise patients and caregivers to measure XATMEP with an accurate milliliter measuring device. A household teaspoon is not an accurate measuring device. Advise patients and caregivers to ask their pharmacist to recommend an appropriate measuring device and for instructions for measuring the correct dose.

Bone Marrow Suppression and Serious Infections

Advise patients to contact their healthcare provider for new onset fever, symptoms of infection, easy bruising or persistent bleeding *[see Warnings and Precautions (5.1, 5.2)]*.

Renal Toxicity

Advise patients that methotrexate can cause renal toxicity *[see Warnings and Precautions (5.3)]*.

Gastrointestinal Toxicity

Advise patients to contact their healthcare provider if they develop diarrhea, vomiting, or stomatitis *[see Warnings and Precautions (5.4)]*.

Hepatic Toxicity

Advise patients concerning the risk of hepatic toxicity and avoidance of alcohol during methotrexate treatment *[see Warnings and Precautions (5.5)]*.

Pulmonary Toxicity

Advise patients to contact their healthcare provider for symptoms of cough, fever, and dyspnea *[see Warnings and Precautions (5.6)].*

Hypersensitivity Reactions

Advise patients concerning the risk for severe hypersensitivity reactions due to XATMEP treatment. These can be fatal and may include severe dermatologic reactions such as toxic epidermal necrolysis, Stevens-Johnson syndrome, exfoliative dermatitis, and erythema multiforme. Advise patients to contact their healthcare provider for signs of a new or worsening rash *[see Warnings and Precautions (5.7)].*

Secondary Malignancies

Advise patients that there is a risk of secondary malignancies during or following treatment with XATMEP *[see Warnings and Precautions (5.8)].*

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 Boxed Warning, Contraindications (4), Warnings and Precautions (5.9), Use in Specific Populations (8.1)]*.

Advise females of reproductive potential to use effective contraception during XATMEP therapy and for 6 months after the final dose *[see Use in Specific Populations (8.3)]*.

Advise males of reproductive potential to use effective contraception during XATMEP therapy and for 3 months after the final dose *[see Use in Specific Populations (8.3)]*.

Ineffective Immunization and Risks Associated with Live Vaccines

Advise patients to avoid receiving vaccines during treatment with XATMEP because they may not be effective and live virus vaccines may cause infection *[see Warnings and Precautions (5.10)]*.

Infertility

Advise patients of reproductive potential that XATMEP may cause impairment of fertility, oligospermia, and menstrual dysfunction *[see Warnings and Precautions (5.11), Use in Specific Populations (8.3)]*.

Lactation

Advise females not to breastfeed during therapy with XATMEP *[see Use in Specific Populations (8.2)]*.

Proper Storage and Disposal

Advise patients to store XATMEP either refrigerated (2°C to 8°C/36°F to 46°F) or at room temperature (20°C to 25°C/68°F to 77°F) with excursions permitted to 15°C to 30°C/59°F to 86°F. If stored at room temperature, discard after 60 days. Inform patients and caregivers of the need for proper storage and disposal of dispensing bottles and dosing devices *[see References (15)]*.

Manufactured for:

azurity pharmaceuticals

Woburn, MA 01801 USA

Patent: *https://azurity.com/patents_and_trademarks/*

This product's label may have been updated. For current Full Prescribing Information, please visit *www.xatmep.com*

REV05

Patient Information
XATMEP® (ZAT-mep)
(methotrexate)
oral solution

What is the most important information I should know about XATMEP?

XATMEP can cause serious side effects that may be severe and lead to death, including:

- **Decreased blood cell counts.** XATMEP can affect your bone marrow and cause decreases in red blood counts, white blood cell counts, and platelets that can be severe and life-threatening. Your healthcare provider will do blood tests before you start XATMEP and at least monthly to check your blood cell counts. Call your healthcare provider right away if you develop any of the following:
  - a new fever
  - symptoms of infection
  - easy bruising or bleeding that will not stop (persistent bleeding)
- **Serious infections.** People who take XATMEP have an increased risk of developing infections that can be life-threatening or cause death. These infections may include: bacterial, fungal, or viral infections, including Pneumocystis *jiroveci* pneumonia, invasive fungal infections, hepatitis B infection that comes back (reactivation), tuberculosis infection that may be new or reactivation, and Herpes zoster or cytomegalovirus (CMV) that spreads throughout the body (disseminated).

  Tell your healthcare provider right away if you develop a new fever or if you have any symptoms of infection during treatment with XATMEP.
- **Kidney problems. Kidney problems, including sudden (acute) kidney failure can happen with XATMEP.**

  Your healthcare provider will do tests to check your kidney function before you start XATMEP and every 1 to 2 months during treatment. **Tell your healthcare provider right away** if you develop any signs or symptoms of kidney problems, including:
  - a big change (either increase or decrease) in the amount of urine you produce
  - swelling in your legs, ankles or feet
  - shortness of breath
  - tiredness
  - weight gain
- **Severe stomach and intestine (gastrointestinal) problems.**
  - Diarrhea, vomiting, nausea, and mouth sores can happen in people who take XATMEP.
  - **Inflammation of the intestine with severe bleeding and a tear in the intestinal wall (perforation) have happened with XATMEP and may cause death.**
  - People who have stomach ulcers (peptic ulcer disease) or ulcerative colitis (UC) have a greater risk of developing severe stomach or intestine problems with XATMEP.
  - Severe stomach and life-threatening intestinal problems can happen when XATMEP is taken with high doses of non-steroidal anti-inflammatory medicines (NSAIDs).

  Tell your healthcare provider if you develop diarrhea, vomiting, or mouth sores during treatment with XATMEP.

  Tell your healthcare provider right away if you develop high fever, shaking chills (rigors), pain in your stomach-area (abdomen) that will not go away or is severe, severe constipation, if you are vomiting blood or have blood in your stools.
- **Liver problems.** XATMEP 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 check your liver function before you start XATMEP and every 1 to 2 months during treatment.
  - Liver function tests that stay abnormal over time may happen without any symptoms of liver problems but can be an early sign of liver fibrosis or cirrhosis.
  - The risk of liver problems increases if you have obesity, diabetes, high cholesterol, current or past liver disease, family history of liver disease, abnormal liver test results, or drink alcohol.

  Tell your healthcare provider if you get any signs or symptoms of liver problems during treatment with XATMEP, including:
  - tiredness
  - easy bleeding or bruising
  - loss of appetite
  - nausea
  - difficulty thinking clearly
  - swelling in your legs, feet or ankles
  - weight loss
  - itchy skin
  - yellowing of your skin or the white part of your eyes
  - weakness

- **Lung problems.** Lung problems can happen suddenly (acute) with XATMEP, or they can develop over a long period-of-time (chronic). Lung problems may not get better (possibly irreversible) and can cause death.
  - Your healthcare provider may do tests to check your lung function during treatment with XATMEP.
  - Tell your healthcare provider if you have any symptoms, including: cough (especially a dry cough), fever, or trouble breathing.
- **Severe allergic and skin reactions.** XATMEP can cause severe skin reactions that can lead to death.
  - XATMEP can cause reactivation of skin reactions that can happen after radiation therapy (radiation recall dermatitis)
  - **Tell your healthcare provider right away about any new or worsening skin rash during treatment with XATMEP.**
  - XATMEP can cause severe allergic reactions. **Do not** take XATMEP if you have had a severe allergic reaction to methotrexate in the past. **Get medical help right away** if you develop any of the following signs or symptoms of a severe allergic reaction during treatment with XATMEP:
    - skin rash, itching and hives
    - swelling of the face, lips, tongue, or throat
    - dizziness
    - trouble breathing
    - wheezing
    - fast heart rate
    - feeling faint
    - stomach-area pain
    - vomiting or diarrhea
- **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 XATMEP to see if you are pregnant.
  - **If you are being treated for a medical condition other than cancer, do not take XATMEP if you are pregnant. See "Who should not take XATMEP?"**
  - If you are taking XATMEP to treat your cancer**,** you and your healthcare provider will decide if you will take XATMEP if you are pregnant.
  - Use effective birth control (contraception) during treatment and for **6** months after your final dose of XATMEP. 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 XATMEP.**

  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 XATMEP.
  - **Tell your healthcare provider right away if your female partner becomes pregnant during treatment with XATMEP.**
- **Risk of death from taking XATMEP the wrong way. XATMEP is taken 1 time each week. Deaths have happened when methotrexate was taken every day instead of 1 time weekly. See "How should I take XATMEP?" for instructions on taking XATMEP correctly.** See "**What are the possible side effects of XATMEP"** for more information about side effects.

What is XATMEP?

XATMEP is a prescription medicine used:

- in combination with other chemotherapy medicines in children, for maintenance treatment of acute lymphoblastic leukemia (ALL)
- to treat children with active polyarticular juvenile idiopathic arthritis (pJIA) when their first treatment, including full dose non-steroidal anti-inflammatory medicines (NSAIDs) did not work well or they could not tolerate them.
- It is not known if XATMEP is safe in people with liver problems.

Do not take XATMEP if you:

- are pregnant and are not being treated for cancer. Pregnant women who do not have cancer should not take XATMEP. XATMEP can cause harm to an unborn baby, including birth defects or death of an unborn baby. See **"What is the most important information I should know about XATMEP?"**
- have or had a severe allergic reaction to methotrexate. See "**What is the most important information I should know about XATMEP?"** See the end of this leaflet for a complete list of ingredients in XATMEP.

Before taking XATMEP tell your healthcare provider about all of your medical conditions, including if you:

- have kidney problems or are receiving dialysis treatments
- have stomach ulcers (peptic ulcer disease)
- have ulcerative colitis

- have or have had liver problems, or a family history or liver problems
- drink alcohol-containing beverages. Tell your healthcare provider if there is any change in the amount of alcoholic beverages you drink during treatment with XATMEP.
- have diabetes
- have lung problems or fluid in your lungs (pleural effusion)
- have recently received or are scheduled to receive a vaccine. You should not receive live vaccines during treatment with XATMEP.
- have fluid in your stomach-area (ascites)
- have had or plan to have radiation treatment
- have low levels of folate (B vitamin)
- plan to have any surgery with general anesthesia, including dental surgery
- are breastfeeding or plan to breastfeed. XATMEP may pass into your breast milk. Do not breastfeed during treatment XATMEP.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements. Taking XATMEP and certain other medicines can affect each other and cause serious side effects. Do not start or change any medicines unless you have talked to your healthcare provider and healthcare provider has told you it is safe.

Know all the medicines that you take and keep a list of them with you at all times to show healthcare providers and pharmacists.

How should I take XATMEP?

- **Take XATMEP exactly as prescribed by your healthcare provider.**
- **Do not** take more XATMEP than prescribed. Do not change your dose of XATMEP unless your healthcare provider tells you to.
- **Take XATMEP by mouth 1 time each week (on the same day each week).**
  - **Do not take XATMEP every day. Severe side effects and death have happened in people who have mistakenly taken methotrexate every day instead of 1 time each week.**
  - **If you are not sure how often to take XATMEP, ask your healthcare provider or pharmacist.**
- Use an accurate dosing device that measures milliliters (mL) to take your prescribed dose of XATMEP.
  - **Do not** use a household teaspoon as it is not an accurate measuring device and can lead to overdose, which can cause serious side effects. Ask your pharmacist for a measuring device and for instructions for measuring the correct dose.
- If you are taking XATMEP for treatment of pJIA, your healthcare provider may have you take folate supplement to help reduce the chance of developing certain side effects, such as mouth sores.
- If you miss a dose of XATMEP, call your healthcare provider for instructions for when to take your next dose of XATMEP.
- If you take too much XATMEP, call your healthcare provider or go to the nearest hospital emergency room right away. You will need to receive a medicine as soon as possible to help reduce side effects that could be severe and could cause death.

What should I avoid while taking XATMEP?

Avoid drinking alcohol during treatment with XATMEP.

What are the possible side effects of XATMEP?

XATMEP can cause serious side effects that may be severe and lead to death including:

- See "**What is the most important information I should know about XATMEP?"**
- **New (secondary) cancers.** New cancers can happen in people who take XATMEP. Certain blood cancers can happen during treatment with XATMEP. In some cases, these blood cancers may completely go away (regress completely) after XATMEP is stopped.
- **Possible fertility problems (infertility) in males and females.** XATMEP can cause fertility problems in males and females, and can cause sperm production to stop in males, and menstrual problems in females. Males may not be able to father a child. Females may not be able to become pregnant. It is not known if your fertility may return. Talk with your healthcare provider about your risk for infertility if this is a concern for you.

The most common side effects of XATMEP include:

- mouth sores
- low white blood cells. **See "What is the most important information I should know about XATMEP?"**
- nausea
- upset stomach
- increased liver function tests

Your healthcare provider may decrease your dose, temporarily stop, or completely stop treatment with XATMEP, if you develop certain side effects.

These are not all the side effects of XATMEP.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800- FDA-1088.

How should I store XATMEP?

- Store XATMEP in the refrigerator between 36°F to 46°F (2°C to 8°C) or at room temperature between 68°F to 77°F (20°C to 25°C).
- If XATMEP is stored at room temperature, throw it away (discard) after 60 days.
- XATMEP comes in a bottle with a child-resistant closure.
- Keep XATMEP bottle tightly closed in its original container.
- Avoid freezing and exposing XATMEP to excessive heat.

Keep XATMEP and all medicines out of the reach of children.

General information about the safe and effective use of XATMEP.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use XATMEP for a condition for which it was not prescribed. Do not give XATMEP to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about XATMEP that is written for healthcare professionals.

What are the ingredients in XATMEP?

Active Ingredient: methotrexate

Inactive Ingredients: purified water, sodium citrate, citric acid, methylparaben sodium, propylparaben sodium, sucralose, and sodium hydroxide or hydrochloric acid (pH adjuster).

Manufactured for: Azurity Pharmaceuticals, Inc. Woburn, MA

For additional information contact Azurity Pharmaceuticals at 1-800-461-7449.

This Patient Information has been approved by the U.S. Food and Drug Administration. Issued: 05/2026