

Patient Information
METHOTREXATE (Meth-oh-trex-ate)
Injection
for intravenous, intramuscular,
subcutaneous, or intrathecal 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.
- **If you are being treated for a medical condition other than cancer, do not receive or take Methotrexate Injection if you are pregnant. See “Do not receive Methotrexate Injection if”.**
- If you are taking Methotrexate Injection to treat your cancer, you and your healthcare provider will decide if you will receive or take Methotrexate Injection 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.

- **In people with psoriasis** who receive Methotrexate Injection, liver fibrosis or cirrhosis may happen without any symptoms or abnormal liver tests. The risk for liver problems in people with psoriasis increases with the amount of Methotrexate Injection that you receive over time.
- 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
- 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

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).
- People who receive injections of Methotrexate Injection into their spine (intrathecal methotrexate) can develop inflammation of the lining around the spinal nerves.

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
- weakness on one side of your body
- sudden blindness that goes away
- seizures
- coma
- headache
- back pain
- 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
- shaking chills
- stomach-area (abdomen) pain that is severe or does not go away
- severe constipation
- if you are vomiting blood
- 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 help prevent (prophylaxis) and to treat leukemia that spreads to the covering of the brain and spinal cord (meninges).
- to treat non-Hodgkin lymphoma
- in combination with other chemotherapy medicines to treat osteosarcoma

in adults:

- in combination with other chemotherapy medicines to treat breast cancer
- alone to treat squamous cell carcinoma of the head and neck
- in combination with other chemotherapy medicines to treat gestational trophoblastic neoplasia

Methotrexate Injection is a prescription medicine used:

- in adults to treat rheumatoid arthritis (RA)
- in children to treat polyarticular juvenile idiopathic arthritis (pJIA)
- in adults to treat severe psoriasis

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?”**
- you are pregnant and are being treated, or will be treated with Methotrexate Injection for rheumatoid arthritis, pJIA, or severe psoriasis, or for any disease other than cancer. Methotrexate Injection 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 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?

- Depending on your medical condition and the dose of Methotrexate Injection that is prescribed by your healthcare

provider, Methotrexate Injection can be given to you:

- through an intravenous (IV) line in your vein
- by injection into a large muscle (intramuscular injection)
- injected under your skin (subcutaneous injection)
- for certain diseases the preservative-free formulation of Methotrexate Injection can also be injected through your spine directly into your spinal fluid.

If you are receiving Methotrexate Injection to treat your cancer:

- Your healthcare provider will decide your dose, how you will receive Methotrexate Injection, 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 are receiving Methotrexate Injection for treatment of severe psoriasis, rheumatoid arthritis, or polyarticular juvenile idiopathic arthritis:

- You should receive your Methotrexate Injection dose 1 time each week, not every day. Serious side effects and death have happened in people who mistakenly have taken Methotrexate every day instead of 1 time each week.
- Take folic acid or folinic acid every day during treatment with Methotrexate Injection, as instructed by your healthcare provider, to help reduce the chance of developing certain side effects, such as mouth sores.
- If you receive too much Methotrexate Injection call your healthcare provider or go to your nearest hospital emergency room right way. You will need to receive a medicine as soon as possible to help reduce side effects that could be severe and could cause death.

In all patients 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?**”
- **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 if you are receiving Methotrexate Injection as a cancer treatment. Your healthcare provider will treat you as needed to prevent or manage TLS if you develop it during treatment with 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 low-dose Methotrexate Injection. In some cases, these blood cancers may completely 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.
- **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
- nausea
- decreased white blood cell count. See “**What is the most important information I should know about Methotrexate Injection?**”
- 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 for Methotrexate Injection Preservative-free: sodium chloride. May contain sodium hydroxide and/or hydrochloric acid 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, Ahmedabad – 380 054, India. For more information call 1-866-941-7875

This Patient Information has been approved by the U.S. Food and Drug Administration.

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