

PART III: CONSUMER INFORMATION

**Pr METHOTREXATE INJECTION, USP
Unpreserved
25 mg/mL (Sterile Solution)**

Read this carefully before you start taking Methotrexate Injection, USP. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about Methotrexate Injection, USP.

ABOUT THIS MEDICATION

What the medication is used for:

Methotrexate Injection, USP belongs to a group of medicines known as antimetabolites. It is used in high doses to treat certain types of cancers, including breast cancer, Non-Hodgkin's lymphoma and leukemia. At lower doses, it may also be used to treat severe psoriasis and severe rheumatoid arthritis.

What it does: Methotrexate Injection, USP works by blocking an enzyme needed by body cells to live. This interferes with the growth of some cells, such as skin cells in psoriasis that are growing rapidly. In rheumatoid arthritis, Methotrexate Injection USP acts on the inflammatory cells that cause joint swelling. Methotrexate Injection, USP therapy is used to control psoriasis and rheumatoid arthritis but it will not cure them. In cancer, Methotrexate Injection, USP works by blocking an enzyme process in cancer cells so that they cannot grow. Some normal cells in the body may be affected as well.

When it should not be used:

Do not take Methotrexate Injection, USP if you:

- Are allergic to any component of the drug.
- Have severe kidney problems.
- Are on dialysis.
- Are pregnant. Methotrexate Injection, USP can cause harm to your unborn baby. Women of childbearing potential should not be started on Methotrexate Injection, USP until pregnancy is excluded.
- Are breast-feeding.
- Have psoriasis or rheumatoid arthritis and the following:
 - alcoholism (drink excessive alcohol)
 - chronic liver disease
 - immunodeficiency (resistance to infectious diseases is reduced)
 - blood disorders

- Are going to receive a general anesthetic called nitrous oxide. It is also known as laughing gas.

What the medicinal ingredient is:

Methotrexate (meth-o-TREX-ate).

What the important nonmedicinal ingredients are:

Hydrochloric acid, sodium chloride, sodium hydroxide and water for injection.

What dosage forms it comes in:

Methotrexate Injection, USP 25 mg/mL comes in the following presentations:

25 mg/mL

50 mg / 2 mL (no preservative) as a single use vial
2 mL vials with brown flip-off aluminum seals

1000 mg / 40 mL (no preservatives) as a single use vial
40 mL vials golden yellow flip-off aluminum seals

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Methotrexate Injection, USP should be prescribed by a doctor who is experienced with the use of antimetabolite therapy.

- Methotrexate Injection, USP can cause serious toxic reactions which may result in death.
- Methotrexate Injection, USP can cause birth defect (deformed babies) or death of an unborn baby when used in pregnant women. Pregnant women with psoriasis or rheumatoid arthritis should not take Methotrexate Injection, USP.

Before you use Methotrexate Injection, USP, talk to your doctor or pharmacist if you have any of the following conditions:

- have or have had any unusual or allergic reaction to Methotrexate Injection, USP.
- are pregnant or planning to become pregnant. Methotrexate can cause birth defects (deformed babies) or death of an unborn baby. Both male and female patients must use effective birth control methods all the time while taking Methotrexate Injection, USP and a few months after the last dose of the drug. Methotrexate may cause sterility (infertility), which could be permanent. Be sure to discuss this with your doctor before taking Methotrexate Injection, USP. Tell your doctor right away if you think you have become pregnant while taking Methotrexate Injection, USP.
- are breast-feeding or plan to breast-feed. Methotrexate may cause serious side effects. Do not breastfeed while you are taking the drug

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- have kidney problems
- have kidney disease
- are dehydrated or have a lot of vomiting, diarrhea, or sweating
- have or have had liver problems, including hepatitis B or hepatitis C infection
- have lung problems
- have problem with your immune system, or infections
- have gastrointestinal problems such as vomiting, diarrhea, mouth sores or inflammation, ulcer, or colitis (ulcer of the intestines)
- have a skin disease
- have a neurologic disorder
- drink alcohol

Methotrexate Injection, USP increases sensitivity to sunlight. Avoid sun exposure and do not use a sunlamp while taking this drug.

Methotrexate can cause sudden bleeding in the lungs. This is called **Pulmonary alveolar haemorrhage**. If you suddenly spit or cough up blood you must go to the hospital right away. You will need emergency care. This occurs in patients with some existing health problems. Some examples are rheumatic disorder (such as pain in your joints) or vasculitis such as swelling in an artery or vein.

Precautions While Using This Medicine

- Do not take Methotrexate Injection, USP daily or more than the dose prescribed. Methotrexate can cause serious toxic reactions which may result in death.
- Do not drink alcohol.
- Do not drive a car or operate machinery until you know how Methotrexate Injection, USP affects you since the drug may cause dizziness and fatigue.
- Drink extra fluid to prevent kidney problems.
- Have regular blood tests to reduce the risk of infection or bleeding. Methotrexate can lower the number of white blood cells and there is an increased risk of infection or bleeding. Talk to your doctor if you need a vaccination. Live vaccines may cause severe infections. Live vaccines or contact with any individual who has had a live vaccination should be avoided, since your ability to fight an infection (immune system) is decreased while taking Methotrexate Injection, USP.

INTERACTIONS WITH THIS MEDICATION

Talk to your healthcare professional about all the medicines you take or have recently taken, including any drugs, vitamins, minerals, natural supplements or

alternative medicines. Methotrexate Injection, USP may interact with the following drugs:

Do not take METHOTREXATE INJECTION, USP if you are going to receive a general anesthetic called nitrous oxide. It is also known as laughing gas. When used together, they can cause:

- Myelosuppression (a condition in which the bone marrow cannot make enough blood cells),
- Mouth sores,
- Inflammation of the mouth,
- Inflammation of the kidneys
- Damage to the nervous system.

- Non-steroidal anti-inflammatory drugs (NSAIDs) and salicylate (acetylsalicylic acid or (ASA)
- Disease Modifying Antirheumatic drugs (DMARDs), such as gold, penicillamine, hydroxychloroquine, or sulfasalazine
- Drugs that may cause harm to the liver (leflunomide, azathioprine, sulfasalazine, retinoid)
- Phenylbutazone
- Phenytoin (to treat seizures)
- Probenecid
- Amphotericin B (may cause harm to kidneys)
- Certain antibiotics such as penicillins, tetracycline, vancomycin, nystatin, neomycin, trimethoprim/sulfamethoxazole, ciprofloxacin, pristinamycin, chloramphenicol
- Theophylline
- Mercaptopurine
- Folic acid or folinic acid
- Cytarabine and other chemotherapy agents
- Radiotherapy
- L-asparaginase, a drug used to treat cancer
- Proton pump inhibitors (PPI). They are drugs used to treat acid-related stomach problems. Some PPIs are omeprazole, esomeprazole, and pantoprazole.
- Pyrimethamine, an anti-parasitic drug
- Nitrous oxide, an inhaled gas used to prevent pain during medical procedures
- Amiodarone, a drug used to treat abnormal heart rhythms
- Sulfonylureas, drugs used to lower blood sugar levels, aminobenzoic acid, sulfonamides, also known as “sulfa drugs”
- Packed red blood cells, used for blood transfusions
- PUVA therapy, a type of ultraviolet light treatment for severe skin conditions
- Triamterene, a drug used to reduce blood pressure and decrease swelling

PROPER USE OF THIS MEDICATION

Methotrexate Injection is for single use only. Any unused product should be discarded by trained personnel.

Take Methotrexate Injection, USP only as directed by your doctor. Do not take more or less of it, and do not take it more often than your doctor ordered. The exact amount of medicine you need has been carefully worked out. Taking too much may increase the chance of side effects, while taking too little may not improve your condition. You should check with your doctor if you are not certain how to take the medication.

- **In most cases, Methotrexate Injection, USP is taken once weekly; the prescribed dose is taken on a single day of the week.**
- **In some cases, your healthcare professional may instruct you to take Methotrexate Injection, USP every 12 hours for 3 doses; you should only do this once a week, and should not take more than 3 doses each week.**
- **It should never be taken every day of the week. When used to treat psoriasis or rheumatoid arthritis. As well, in most cases of cancer, Methotrexate Injection, USP should not be taken every day of the week.**
- **Taking Methotrexate Injection, USP daily, or in a dose larger than prescribed can result in serious complications, often requiring hospitalization, and sometimes resulting in death. Taking even small doses of Methotrexate Injection, USP daily for less than a week can result in serious consequences, including death.**
- Select a day of the week when you are most likely to remember to take Methotrexate Injection, USP, and take it on that same day each week.
- Each time you refill your prescription, check to see whether the dose you need to take has changed.

Methotrexate Injection, USP is often given together with certain other medicines. If you are using a combination of medicines, make sure that you take each one at the proper time and do not mix them. Ask your doctor or pharmacist to help you plan a way to remember to take your medicines at the right times.

While you are using Methotrexate Injection, USP, your doctor may want you to drink extra fluids so that you will pass more urine. This will help the drug to pass from the body, and will prevent kidney problems and keep your kidneys working well.

If you vomit shortly after taking a dose of Methotrexate Injection, USP, check with your doctor. You will be told whether to take the dose again or to wait until the next scheduled dose.

Usual dose:

The dose of Methotrexate Injection, USP will be different for different patients. The dose that is used may depend on a number of things, including what the medicine is being used for, the patient's size, and whether or not other medicines are also being taken. If you are taking or receiving Methotrexate Injection, USP at home, follow your doctor's orders or the directions on the label. If you have any questions about the proper dose of Methotrexate Injection, USP, ask your doctor. The doctor may decrease your dose if you have problems with your kidneys.

Overdose:

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately

- Do this even if you have no signs of discomfort.

Missed dose:

- If you missed a scheduled dose, contact your doctor for instruction.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Along with their needed effects, medicines like Methotrexate Injection, USP can sometimes cause unwanted effects. Also, because of the way these medicines act on the body, there is a chance that they might cause other unwanted effects that may not occur until months or years after the medicine is used. These delayed effects may include certain types of cancer, such as leukemia. Discuss these possible effects with your doctor.

Methotrexate Injection, USP commonly causes nausea and vomiting. Even if you begin to feel ill, do not stop using this medicine without first checking with your doctor. Ask your doctor for ways to lessen these effects.

The most common side effects include:

- Upset stomach, stomach pain, vomiting, nausea, loss of appetite, dizziness, chills and fever, diarrhea or sores on lips or mouth
- A fall in the number of white blood cells. This may reduce your resistance to infection and increase your chances of cold sores, blood poisoning or swelling of blood vessels
- Tiredness (fatigue)

Less common side effects are:

IMPORTANT: PLEASE READ

- Headaches, hair loss, mood changes, confusion, ringing in the ears, sore eyes, skin rashes, increased sensitivity to sunlight or unexplained weight loss
- A fall in the number of other blood cells. This may increase your chances of bruising, bleeding or tiredness
- Damage to the lungs
- Harm to the unborn baby
- Convulsions

Rarely, Methotrexate Injection, USP can cause other side effects including:

- Liver damage, kidney damage, pain or difficulty urinating, lower back or side pain, blood in urine or stools, dark urine
- Fits, blurred vision, short term blindness
- Drowsiness, weakness
- Hoarseness
- Bloody vomit, black, tarry stools or pin-point red spots on the skin
- Reddening or whitening of the skin, acne, boils, itching yellow skin or eyes
- Impotence or loss of interest in sex, decreased fertility, abortion
- Diabetes, thinning of the bones, painful muscles and joints
- Low blood pressure
- Gastrointestinal ulcers

More rarely, it can cause:

- Skin rash and other skin disorders
- Cancer of lymph glands, sudden death
- Severe allergic reactions
- Leukoencephalopathy
- Damage to heart

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Diarrhea, vomiting, abdominal pain, or mouth ulcers			√
	Sore throat, fever, chills, or swelling of glands		√	
	Inflammation of the lungs: Persistent dry, non-productive cough, shortness of breath and		√	

	fever.			
Less common	Chest pain, cough, shortness of breath or fever			√
	Unusual bleeding or bruising			√
	Severe headaches			√
Rare	Signs of severe allergic reaction: Skin rash, itching, chest tightness, wheezing, dizziness, hives, faintness, rapid heartbeat, shortness of breath, and/or a swollen face, lips or tongue			√
	Pain or difficulty urinating, lower back or side pain, blood in urine or stools, dark urine		√	
	Yellow colour of eyes or skin			√
	Renal Failure/ kidney damage (inability of the kidneys to work properly): Swelling of the hands, ankles or feet. Nausea, vomiting. Blood in the urine. Changes in frequency or amount of urine.			√
Unknown	Gastrointestinal Related: Severe abdominal pain, tenderness, chills, fever, nausea, vomiting, extreme thirst, difficulty passing urine or bowel movement			√
	Central Nervous System Related: Behaviour changes, decreased			√

consciousness, headache, weakness, numbness, vision loss or double vision, seizures, vomiting, loss of memory			
DRESS (allergic reactions): Fever, rash, hives, swelling of eyes, lips or tongue			√
Pulmonary alveolar haemorrhage: suddenly spit or cough up blood			√

This is not a complete list of side effects. For any unexpected effects while taking Methotrexate Injection, USP, contact your doctor or pharmacist.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about Methotrexate Injection, USP:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (<https://health-products.canada.ca/dpd-bdpp/index-eng.jsp>); or by calling 1-844-596-9526

This leaflet was prepared by Mylan Pharmaceuticals ULC Etobicoke, Ontario M8Z 2S6

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HOW TO STORE IT

- Keep out of the reach and sight of children.
- Store it between 15°C to 25°C and away from heat.
- Protect from light. Avoid freezing Methotrexate Injection, USP.
- Methotrexate Injection, USP should not be used beyond the labeled expiry date.
- Do not keep outdated medicine or medicine no longer needed. Be sure that any discarded medicine is out of the reach of children.