Methotrexate (Mexate®, Folex®, Rheumatrex®, Amethopterin, MTX)

Pronounced: meth-oh-TREK-sate
Classification: Antimetabolite

About Methotrexate (Mexate®, Folex®, Rheumatrex®, Amethopterin, MTX)
Methotrexate interferes with DNA production. This stops cell growth and division, resulting in the slowing or stopping of cancer growth. Since cancer cells, in general, divide faster and with less error-correcting than healthy cells, cancer cells are more sensitive to this damage. Methotrexate competes with folic acid uptake in cells. This results in a folic acid deficiency in these cells and leads to cell death. By affecting the folic acid uptake, methotrexate also alters DNA replication and cell division. Cancer cells take up methotrexate faster than normal cells (because they are rapidly dividing and thus replicate their DNA more frequently), causing their cell death.

Leucovorin is given starting 24 hours after methotrexate. Leucovorin is also known as folinic acid and is converted into a derivative of folic acid in the body. Therefore, Leucovorin is given in an attempt to prevent healthy cells from taking up too much methotrexate, but on the other hand, allowing time for the methotrexate to get into cancer cells to cause their death.

How to Take Methotrexate
Methotrexate is given by intravenous (IV) infusion. In special situations, it may be injected into the spinal cord space (called intrathecal administration). It can also be given by mouth in the form of a tablet. The dosage is based on your body weight, medical condition, and the regimen your physician is using.

*If you have been prescribed leucovorin in combination with methotrexate and are unable to take it, keep it down, or miss a dose, call your healthcare team immediately.

The blood levels of this medication can be affected by certain foods and medications, so they should be avoided. These include non-steroidal anti-inflammatory (NSAID) medications including ibuprofen, tetracycline, penicillin, sulfamethoxazole/trimethoprim, some other oral antibiotics, and folic acid. Be sure to tell your healthcare provider about all medications and supplements you take.

You, or anyone you live with, should avoid having live or live-attenuated vaccines while receiving this medication. These include herpes zoster (Zostavax) for shingles prevention, oral polio, measles, nasal flu vaccine (FluMist®), rotavirus, and yellow fever vaccines.

Possible Side Effects of Methotrexate
There are a number of things you can do to manage the side effects of Methotrexate. Talk to your care team about these recommendations. They can help you decide what will work best for you. These are some of the most common or important side effects:

**Infection and Low White Blood Cell Count (Leukopenia or Neutropenia)**
This medication can cause life-threatening infections, with or without a decrease in white blood cell counts.

White blood cells (WBC) are important for fighting infection. While receiving treatment, your WBC count can drop, putting you at
a higher risk of getting an infection. You should let your doctor or nurse know right away if you have a fever (temperature greater than 100.4 °F or 38 °C), sore throat or cold, shortness of breath, cough, burning with urination, or a sore that doesn’t heal.

Tips to preventing infection:

- **Washing hands**, both yours and your visitors, is the best way to prevent the spread of infection.
- Avoid large crowds and people who are sick (i.e.: those who have a cold, fever, or cough or live with someone with these symptoms).
- When working in your yard, wear protective clothing including long pants and gloves.
- Do not handle pet waste.
- Keep all cuts or scratches clean.
- Shower or bath daily and perform frequent mouth care.
- Do not cut cuticles or ingrown nails. You may wear nail polish, but not fake nails.
- Ask your oncology care team before scheduling dental appointments or procedures.
- Ask your oncology care team before you, or someone you live with has any vaccinations.

**Nausea and/or Vomiting**

Talk to your oncology care team so they can prescribe medications to help you manage nausea and vomiting. In addition, dietary changes may help. Avoid things that may worsen the symptoms, such as heavy or greasy/fatty, spicy or acidic foods (lemons, tomatoes, oranges). Try saltines, or ginger ale to lessen symptoms.

Call your oncology care team if you are unable to keep fluids down for more than 12 hours or if you feel lightheaded or dizzy at any time.

**Mouth Sores (Mucositis)**

Certain cancer treatments can cause sores or soreness in your mouth and/or throat. Notify your oncology care team if your mouth, tongue, inside of your cheek or throat becomes white, ulcerated, or painful. Performing regular mouth care can help prevent or manage mouth sores. If mouth sores become painful, your doctor or nurse can recommend a pain reliever.

- Brush with a soft-bristle toothbrush or cotton swab twice a day.
- Avoid mouthwashes that contain alcohol. A baking soda and/or salt with warm water mouth rinse (2 level teaspoons of baking soda or 1 level teaspoon of salt in an eight-ounce glass of warm water) is recommended 4 times daily.
- If your mouth becomes dry, eat moist foods, drink plenty of fluids (6-8 glasses), and suck on sugarless hard candy.
- Avoid smoking and chewing tobacco, drinking alcoholic beverages, and citrus juices.

**Diarrhea**

Your oncology team can recommend medications to relieve diarrhea. Also, try eating low-fiber, bland foods, such as white rice and boiled or baked chicken. Avoid raw fruits, vegetables, whole-grain breads, cereals, and seeds. Soluble fiber is found in some foods and absorbs fluid, which can help relieve diarrhea. Foods high in soluble fiber include applesauce, bananas (ripe), canned fruit, orange sections, boiled potatoes, white rice, products made with white flour, oatmeal, cream of rice, cream of wheat, and farina. Drink 8-10 glasses of non-alcoholic, un-caffeinated fluid a day to prevent dehydration.

**Low Red Blood Cell Count (Anemia)**

Your red blood cells are responsible for carrying oxygen to the tissues in your body. When the red cell count is low, you may feel tired or weak. You should let your oncology care team know if you experience any shortness of breath, difficulty breathing or pain in your chest. If the count gets too low, you may receive a blood transfusion.

**Low Platelet Count (Thrombocytopenia)**

Platelets help your blood clot, so when the count is low you are at a higher risk of bleeding. Let your oncology care team know if you have any excess bruising or bleeding, including nose bleeds, bleeding gums or blood in your urine or stool. If the platelet count becomes too low, you may receive a transfusion of platelets.

- Do not use a razor (an electric razor is fine).
Avoid contact sports and activities that can result in injury or bleeding.

- Do not take aspirin (salicylic acid), non-steroidal, anti-inflammatory medications (NSAIDs) such as Motrin/Advil (ibuprofen), Aleve (naproxen), Celebrex (celecoxib), etc. as these can all increase the risk of bleeding. Please consult with your healthcare team regarding the use of these agents and all over-the-counter medications/supplements while on therapy.
- Do not floss or use toothpicks and use a soft-bristle toothbrush to brush your teeth.

**Fatigue**

Fatigue is very common during cancer treatment and is an overwhelming feeling of exhaustion that is not usually relieved by rest. While on cancer treatment, and for a period after, you may need to adjust your schedule to manage fatigue. Plan times to rest during the day and conserve energy for more important activities. Exercise can help combat fatigue; a simple daily walk with a friend can help. Talk to your healthcare team for helpful tips on dealing with this side effect.

**Loss or Thinning of Scalp and Body Hair (Alopecia)**

Your hair may become thin, brittle, or may fall out. This typically begins two to three weeks after treatment starts. This hair loss can be all body hair, including pubic, underarm, legs/arms, eyelashes, and nose hairs. The use of scarves, wigs, hats, and hairpieces may help. Hair generally starts to regrow soon after treatment is completed. Remember your hair helps keep you warm in cold weather, so a hat is particularly important in cold weather or to protect you from the sun.

**Nail and Skin Changes**

Your fingernails/toenails may become dark, brittle, or fall off. Keep your fingernails and toenails clean and dry. You may use nail polish, but do not wear fake nails (gels, acrylics, overlay). If any nails fall off, clean the nail bed well with soap and water and cover with a band-aid.

You may notice dry skin or changes in the color or tone of your skin. Your skin may be more sensitive to the sun, which can result in severe sunburn or rash. Sun sensitivity can last even after chemotherapy is completed. Avoid the sun between 10-2 pm, when it is strongest. Wear sunscreen (at least SPF 30 with UVA/UVB protection) every day and reapply when in the sun for extended periods of time; wear sunglasses with UVA/UVB protection, a hat, and long sleeves/pants to protect your skin and seek out shade whenever possible.

**Secondary Malignancies**

There is a very low risk of developing leukemia, sarcoma, lung cancer, or other types of cancer due to treatment with this medication, which can occur many years after treatment. This is most often associated with repeated treatments or high doses.

**Kidney Problems**

This medication can cause kidney problems, including an increased creatinine level, which your oncology care team may monitor for using blood tests. Notify your healthcare provider if you notice decreased urine output, blood in the urine, swelling in the ankles, or loss of appetite.

**Tumor Lysis Syndrome**

If there are a large number of tumor cells in your body prior to treatment, you are at risk for tumor lysis syndrome. This happens when the tumor cells die too quickly and their waste overwhelms the body. You may be given a medication (allopurinol) and IV fluids to help prevent this. If you experience nausea, vomiting, diarrhea, or become lethargic (drowsy, sluggish), notify your oncology team right away. TLS can affect your kidney function. Your provider will monitor your kidney function with blood work. Notify your provider if you have little or no urine output.

**Radiation Recall**

Radiation recall is when the administration of a medication causes a skin reaction that looks like a sunburn (redness, swelling, soreness, peeling skin) in areas where radiation was previously given. Notify your oncology team if you notice this side effect. Treatment can include topical steroid ointments and a delay in your next chemotherapy dose.

**Less common, but important side effects can include:**
**Lung Changes:** This medication can cause an opportunistic infection called pneumocystis pneumonia. It can also cause interstitial pneumonitis, particularly when high doses have been received. Interstitial pneumonitis can develop months to years after treatment is completed and may be more common in people with pre-existing lung conditions. Notify your healthcare provider if you develop fever, shortness of breath, non-productive cough, wheezing, or difficulty breathing.

**Liver Toxicity:** This medication can cause liver toxicity, which your oncology care team may monitor for using blood tests called liver function tests. Notify your healthcare provider if you notice yellowing of the skin or eyes, your urine appears dark or brown, or you have pain in your abdomen, as these can be signs of liver toxicity.

**Eye Problems:** This medication can cause your eyes to become irritated or watery and you may be more sensitive to light. Notify your provider if you develop any eye changes.

**Neurologic changes:** This medication can affect the nervous system, causing you to feel drowsy, dizzy, or confused. Notify your provider if you are feeling different.

**Sexual & Reproductive Concerns**

This medication may affect your reproductive system, resulting in the menstrual cycle or sperm production becoming irregular or stopping permanently. Women may experience menopausal effects including hot flashes and vaginal dryness. In addition, the desire for sex may decrease during treatment. You may want to consider sperm banking or egg harvesting if you may wish to have a child in the future. Discuss these options with your oncology team.

Exposure of an unborn child to this medication could cause birth defects, so you should not become pregnant or father a child while on this medication. Effective birth control is necessary during treatment and for at least 3 months after treatment for men and during treatment and for at least 6 months for women, even if your menstrual cycle stops or you believe you are not producing sperm. You should not breastfeed while receiving this medication.

**Intrathecal (Spinal) Administration**

When injected into the spinal cord space, methotrexate can cause headache, vomiting, fever or stiff neck. In rare cases, intrathecal administration can cause neurotoxicity, which presents with paralysis, speech difficulty, seizures, or coma. This can occur up to several days after the treatment and resolves in a few days.