METHOTREXATE

INSTRUCTIONS FOR THE PHARMACIST

Prescription

- All orders *for cancer patients* written on a **pre-printed order**; if not, compare prescription to standard regimens in the Systemic Therapy Manual to confirm the dosing and instructions
  - The order must be signed by BOTH the prescriber (at the bottom) AND at least one other oncology health professional (nurse or hospital pharmacist) who has verified the order
- The prescription may **not** be refilled (unless specifically ordered by the oncologist) and it may **not** be filled as a continuing care prescription (*for oncology indications*)
  - If the prescriber has written for refills, do **not** dispense until the oncology team authorizes the refill; Blood work must be checked for each cycle.
- Always check for drug-drug interactions, especially before the first cycle, as described below. Consult the **Drug Interactions** section (page 4), and consider an online drug interactions checking program.
- Check with patient for any other medications filled at a different pharmacy

Handling and Dispensing

- When handling this drug, disposable gloves should be worn at all times by any woman of child-bearing potential. Counting trays and other equipment directly exposed to the drug should be cleaned with **soap and water (not alcohol**), followed by rinsing with copious amounts of water (wear gloves).
- Do not crush tablets in an open air environment and risk inhalation of powder.
- ALWAYS affix the auxiliary label to identify this medication as "Cancer Chemotherapy"-

Patient Counseling and Follow-up

- Counsel the patient, including the key messages listed below. Use the **Initial Assessment and Patient Counseling Visit- Pharmacist Guide❶** and the **Medication Info Sheet❷** for this drug. Be sure that you know the specific treatment schedule and that this is clearly communicated to the patient.
- Call the patient within the first week to identify any problems with adverse reactions or adherence.
  - When speaking with the patient and during call backs, ask the patient to identify any problems with medication adherence. Use the **First Follow-Up Call/Visit- Pharmacist Guide❶**.
- Continuing follow up calls between clinic visits are necessary for ADR identification and prevention and for adherence management. Contact the oncology clinic nurse or hospital pharmacist to negotiate who will do follow-up calls between clinic visits. Tell the patient that you plan to call back to check on their progress. Consider the suggested call-back schedule (pg. 2), with specific questions for each contact.
  - When speaking with the patient and during call backs, ask the patient to identify any problems with medication adherence. Use the **Continuing Follow-Up Calls/Visits - Pharmacist Guide❶**.
- If the patient reports any adverse effects, consider the management strategies suggested in the **Adverse Drug Reaction Management Guide❷**.

- ALWAYS document your findings in the patient profile of your pharmacy computer system
- ALWAYS contact the patient's cancer care team of any findings and actions you have taken.
- ALWAYS **watch for any unusual or unexpected symptoms or problems** (such as an adverse reaction that appears too soon or too severe) and contact the cancer care team promptly if something seems wrong with the patient experience.

CLINICAL INDICATIONS

Methotrexate is clinically indicated for several different cancer, and non-cancer indications, including:

- Acute lymphocytic leukemia
- Choriocarcinoma
- Non-Hodgkin's lymphoma
- Mycosis fungoides
- Graft vs. host disease (prophylaxis)

DRUG ADMINISTRATION

- Methotrexate may be given on a single day or over several days. Rest periods of at least one week are given between each course.
- Methotrexate should not be taken with food, especially milk-rich foods. This decrease serum concentrations of the drug. Folate may decrease drug response.
- Patients should not consume alcohol while taking Methotrexate. Patients should limit their caffeine intake while taking Methotrexate.
- Swallow whole tablets with a glass of water- Do not crush, split, or dissolve the tablets.
- Keep out of reach of children.
- If a dose is missed, do not take a double dose the next day to make up for it.

PATIENT COUNSELLING- INITIAL AND FOLLOW-UP CALLS

- In addition to other printed materials, use the **Medication Info Sheet** from the Cancer Care Nova Scotia website, and consider the more detailed suggestions in this toolkit.

	Key Messages
Initial counselling- At time of dispensing	• How to take the medication properly (including treatment-free breaks) • Good oral hygiene • When to call back to the cancer care team for urgent care • Use the **Initial Assessment and Patient Counseling Visit- Pharmacist Guide❶** and the drug-specific **Medication Info Sheet❷**
First call-back – Within first week: 	• Identify any initial problems with understanding or adherence • Use the **First Follow-Up Call/Visit- Pharmacist Guide❶** and the **Medication Info Sheet❷** (if needed) • Reinforce initial key messages o How and when treatment is taken o Barriers to adherence- remembering to take medication; reluctance to take treatment; financial issues; nausea, vomiting or other adverse effects; trouble with packaging; felt better off medication; other concerns o Suggest strategies to ensure adherence; reminder that full dose is needed for cancer control- partial doses may be ineffective. • Identify any early adverse effect symptoms; suggest management strategies
Second call-back – After 2-4 weeks: (telephone or return visit to Pharmacy) 	• Ask if there are any pills left over and, if so, PROBE to determine any barriers to treatment adherence (see above) • Identify any adverse effects (**PROBE** for evidence of any adverse effect- see below) • Use the **Continuing Follow-Up Calls/Visits- Pharmacist Guide❶** o If any identified, contact oncologist or oncology nurse • Reinforce oral hygiene measures (**PROBE** to ensure patient is following proper measures)

	• Reinforce initial key messages
Subsequent cycles- (at least one call during each cycle:	• Negotiate with patient and cancer care team for ongoing needs for counseling and timely follow up calls • Use the **Continuing Follow-Up Calls/Visits- Pharmacist Guide❶** • Adherence assessment and support is an important issue for reinforcement at each visit and mid-cycle call-back as treatment continues

ADVERSE EFFECTS: PREVENTION AND MANAGEMENT SUGGESTIONS

If you identify any of the following, you should contact the oncologist and tell the patient to call the oncologist or go directly to the Emergency Department of the nearest hospital right away🗲:

- Hypersensitivity reaction (hives; difficulty breathing; swelling of face, lips, tongue, or throat)
- Seizures
- Blood in urine or stools
- Symptoms of infection (fever, chills, body aches, flu symptoms)
- Pale skin, easy bruising, unusual bleeding, weakness, feeling light-headed or short of breath
- Symptoms of hepatotoxicity (nausea, upper stomach pain, itching, loss of appetite, dark urine, clay-coloured stools, yellow skin or eyes)
- Severe skin reaction (fever, sore throat, swelling in face or tongue, burning eyes, painful skin, red or purple skin rash that spreads and causes skin to blister or peel)

The following are the common adverse effects from Methotrexate.

More Common	**Less Common**
<u>Blood disorders</u> • Low white blood cell (neutropenia) and platelet (thrombocytopenia) counts✶ <u>Gastrointestinal disorders</u> • Stomatitis- sores in the mouth or on lips✶ • Elevated liver function tests♦ <u>General disorders</u> • Loss of appetite <u>Bleeding disorders</u> • Unusual bruising or bleeding♦ • Black, tar-like bowel movements♦ • Red spots on skin♦	<u>Gastrointestinal disorders</u> • Nausea✶, vomiting✶, diarrhea✶ • Hepatotoxicity (rare) 🗲 <u>Skin disorders</u> • Skin rash✶, itch✶, photosensitivity✶ • Swollen or painful skin where radiation treatment was given♦ <u>General disorders</u> • Hair loss (from head and body) ✶ • Infection (fever, chills, cough, sore throat) ♦ - severe🗲 • Seizures🗲

✶ For detailed recommendations on the management of these adverse drug reactions, see the **Adverse Drug Reaction Management Guide❷**

♦ For management of these symptoms, the patient should see his physician

🗲 These symptoms require urgent attention- advise the patient to go to the Emergency Department or contact their doctor (see instructions above)

DRUG INTERACTIONS

Take a ***thorough medication history*** (call other pharmacies if necessary) and determine the potential for all other drugs to increase or decrease Methotrexate plasma concentration.

- Drug interactions are often missed by community pharmacy computer systems
- ***REPORT any potential interaction*** to the prescribing oncologist- either the Methotrexate or the interaction drug may need to be dose altered or discontinued.

LIST OF IMPORTANT DRUG-DRUG INTERACTIONS WITH Methotrexate- *This is not a complete list*

* Drinking alcohol while taking Methotrexate increases hepatotoxicity and should be avoided.

- Acitretin: may increase hepatotoxicity of Methotrexate (avoid combination)
- Alitretinoin (systemic): may increase hepatotoxicity of Methotrexate
- BCG: Methotrexate may decrease therapeutic effect of BCG (avoid combination)
- Bile acid sequestrants: may decrease absorption of Methotrexate
- **Ciprofloxacin** (systemic): may increase the serum concentration of Methotrexate
- CloZAPine: Methotrexate may enhance the toxicity of CloZAPine, especially agranulocytosis. (avoid combination)
- Cyclosporine (systemic): may increase the serum concentration of Methotrexate. This may cause vomiting, oral ulcers, hepatotoxicity and/or nephrotoxicity. Methotrexate may increase the serum concentration of Cyclosporine. This may result in nephrotoxicity. (consider therapy modification)
- Denosumab: may enhance the toxicity of Methotrexate, especially the risk for serious infections
- Digoxin: Methotrexate may decrease absorption of Digoxin.
- Echinacea: may diminish the therapeutic effect of Methotrexate, because Echinacea may stimulate the immune system. Do not take Echinacea.
- Eltrombopag: may increase the serum concentration of OATP1B1/SLCO1B1 substrates. Consideration of a preventative dose reduction may be warranted. (Consider therapy modification)
- **Leflunomide**: Methotrexate may increase the toxicity of Leflunomide, especially the risk of pancytopenia and/or hepatotoxicity
- Loop diuretics (e.g. furosemide): Methotrexate may diminish the therapeutic effect of loop diuretics. Methotrexate may increase the serum concentration of these drugs. Loop diuretics may also increase the serum concentration of Methotrexate. Monitor for increased Methotrexate and/or loop diuretic levels/toxicity and monitor for decrease therapeutic effect of loop diuretic. Dose reductions may be needed.
- **NSAIDs**: may increase the serum concentration of Methotrexate (Consider therapy modification)
- **Penicillins**: may increase the serum concentration of Methotrexate
- P-glycoprotein/ABCB1 Inducers: may decrease the serum concentration of P-glycoprotein substrates, and may also limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large quantities (brain, T cells, testes, etc.)
- P-glycoprotein/ABCB1 Inhibitors: may increase the serum concentration of P-glycoprotein/ABCB1 substrates. P-glycoprotein inhibitors may also increase the distribution of p-glycoprotein substrates to specific cells, tissues, or organs where p-glycoprotein is found in large amounts.
- Phenytoin, Fosphenytoin: Methotrexate may decrease the serum concentration of Fosphenytoin-Phenytoin
- **Probenecid**: may increase serum concentration of Methotrexate (Avoid combination if possible, and consider lower Methotrexate doses/monitor for toxicity if used concomitantly.)
- Proton Pump Inhibitors: may increase serum concentration of Methotrexate
- Roflumilast: may increase immunosuppressive effect of Methotrexate (Consider therapy modification)

- Salicylates: may increase serum concentration of Methotrexate. Doses used for prophylaxos of cardiovascular events are not likely of concern.
- Sapropterin: Methotrexate may decrease serum concentration of Sapropterin (may decrease tissue concentrations of tetrahydrobiopterin.
- SulfaSALAzine: may increase hepatotoxicity of Methotrexate
- **Sulfonamide antibiotics**: may increase the toxicity of Methotrexate. Consider avoiding concomitant use of Methotrexate and either sulfamethoxazole or trimethoprim. If used together, monitor for Methotrexate toxicity (e.g. bone marrow suppression).
- Tacrolimus (topical): may increase toxicity of Methotrexate (avoid combination)
- Theophylline derivatives: Methotrexate may increase serum concentration of these drugs
- Trastuzumab: may increase the neutropenic effect of Methotrexate
- Vaccines (inactivated): Methotrexate may diminish the effect of vaccines
- Vaccines (live): Methotrexate may increase the toxicity of live vaccinations
- Vitamin supplements containing folic acid: may decrease Methotrexate levels (avoid combination)
- Vitamin K Antagonists (e.g. Warfarin): Methotrexate may increase/decrease the anticoagulant effect of these drugs.

It is strongly recommended that you check any concurrent medications for interactions with this oral chemotherapy agent. Try one of the following comprehensive programs for checking drug interactions.

Online Programs for Drug Interaction Checking-Publicly available:	**Other Interaction Checkers-Subscription required**:
• http://www.drugs.com/drug_interactions.php • http://reference.medscape.com/drug-interactionchecker • http://www.healthline.com/druginteractions • http://cpref.goldstandard.com/inter.asp?r=8084 • http://umm.edu/health/medical/drug-interaction-tool • http://online.epocrates.com/ (free account required)	• Lexicomp • Micromedex • eCPS