Medicines containing Methotrexate

Educational Materials for Healthcare Professionals

To minimise the risk of overdose from patients incorrectly taking methotrexate daily instead of once weekly for autoimmune diseases

Medicines containing methotrexate are available in a range of presentations, including; oral tablets, oral solutions, vials for injection, pre-filled syringes and pens for injection, concentrate for solution for injection.

Medicines containing methotrexate are used in two sets of indications:

- Autoimmune conditions including, rheumatoid arthritis, psoriasis and Crohn's disease
- Oncology

Please consult the Summary of Product Characteristics (SmPC) of individual products for full prescribing information. This document should be read in conjunction with other relevant clinical guidance on the prescribing and dispensing of methotrexate.

Patients with autoimmune diseases must be told that methotrexate must only be taken once a week.

Patients should be advised to write the treatment day on their Patient Reminder Card, and to carry it with them.

For the treatment of cancer, the frequency depends on the regimen and can require daily administration of methotrexate.

Healthcare professionals and patients must be clearly told that incorrect use of methotrexate can result in severe adverse reactions and even death.

Purpose of this guide

- To inform about the potential for fatal overdose due to medication errors, including daily instead of once weekly use
- To highlight the need to inform patients and others about once weekly dosing
- To provide information on the importance of writing prescriptions with clear instructions about once weekly dosing, defined day of intake, and not to use abbreviations.
- To remind pharmacists to counsel the patient about accidental overdosing

It is recognised that medication errors can sometimes happen despite appropriate prescribing and patient/carer instruction. Therefore this guide also describes the risks and what to do in the event of a medication error.

September 2022

What are the risks associated with overdose?

In post marketing experience with methotrexate, reports of overdose that indicate accidental daily administration instead of weekly is associated with a risk of serious harm. Symptoms commonly reported following oral overdose include leukopenia, thrombocytopenia, anaemia, pancytopenia, bone marrow suppression, mucositis, stomatitis, oral ulceration, nausea, vomiting, gastrointestinal ulceration and gastrointestinal bleeding.

There have been reports of death following overdose due to methotrexate medication errors. In these cases, events such as sepsis or septic shock, renal failure, and aplastic anaemia were also reported.

Considering home or self-administration

It is the responsibility of the prescribing physician to determine which patients are suitable for home or self-administration of medicines containing methotrexate.

Patients who are taking methotrexate for arthritis or psoriasis should be made aware of the importance of this medicine being taken once weekly and the risk of serious adverse reactions including death if taken more frequently.

What should I discuss with my patients?

It is important to discuss signs and symptoms of adverse reactions with the patient, which will enable them to recognise possible events of overdose.

It is very important to remind patients who are being treated for autoimmune diseases and their carers to be sure that they understand:

- Only to take methotrexate once a week
- Which day of the week the dose should be taken. The prescriber and patient/carer should decide this together. The day of the week should be written down in full on the prescription by the prescriber
- That greater doses or higher frequencies are associated with an increased risk of serious adverse events, including death
- If they do make a mistake to record and report to their doctor or pharmacist what they have taken and when

Prescribing & dispensing requirements

Please do not use medical abbreviations or shorthand on the prescription.

For once weekly dosing regimens:

- Include on the prescription the defined day of intake as well as clear instructions on once weekly dosing.

- On dispensing the pharmacist should transcribe the defined day of the week for intake onto the patient card provided with the tablets (found either on the outer package or inside the box) and on the outer packaging. The pharmacist should show the patient card to the patient/carer, reiterate the once weekly dosing schedule and the other elements described on the patient card.

Follow-up visits and medication errors

Patients should be monitored for signs and symptoms of overdose (these predominantly affect the haematopoietic and gastrointestinal systems), such as bleeding, unusual feeling of weakness, ulcers in the mouth, feeling sick, vomiting, black or bloody stools, coughing up blood or vomiting blood and reduced urine output.

Therapeutic management of overdose

If the patient is not already in a clinical setting then they should immediately go to their local Emergency Department bringing their medication, including the packaging. On arrival they should present their medication and tell the reception/registration desk that they are taking methotrexate and have been instructed by the prescriber that immediate treatment is required in the event of an overdose.

Calcium folinate is the specific antidote for neutralising the adverse toxic effects of methotrexate. In the event of overdose, a dose of calcium folinate equal to or higher than the offending dose of methotrexate should be administered intravenously or intramuscularly within 1 hour, and dosing continued until serum level of methotrexate are below 10^{-7} mol/L.

In the event of a large overdose, hydration and alkalinisation of the urine may be required to prevent precipitation of methotrexate and/or its metabolites in the renal tubules. Neither haemodialysis nor peritoneal dialysis has been shown to improve the elimination of methotrexate. Effective clearance of methotrexate is reported to be achieved with acute intermittent haemodialysis using a high-flux dialyser.

Reporting of Adverse Reactions

Please continue to report suspected side effects to the MHRA through the Yellow Card Scheme. Please report:

- all suspected side effects that are serious or result in harm. Serious reactions are those that are fatal, life-threatening, disabling or incapacitating, those that cause a congenital abnormality or result in hospitalisation, and those that are considered medically significant for any other reason
- all suspected side effects associated with new drugs and vaccines identified by the black triangle▼
- It is easiest and quickest to report side effects online via the Yellow Cards website - https://yellowcard.mhra.gov.uk/ or via the Yellow Card app available from the Apple App Store or Google Play Store.

Alternatively, prepaid Yellow Cards for reporting are available by writing to FREEPOST YELLOW CARD (no other address details necessary); by emailing yellowcard@mhra.gov.uk; at the back of the British National Formulary (BNF); by telephoning the Commission on Human Medicines (CHM) free phone line: 0800-731-6789; or by downloading and printing a form from the Yellow Card website.