NHS
Pan Mersey
Area Prescribing Committee

METHOTREXATE: safe prescribing and dispensing

SAFETY

Methotrexate is authorised in the UK for two different groups of indications, each of them with a different administration schedule:

- For the treatment of cancer, in which frequency depends on the regimen and which can require daily administration of methotrexate.
- For the treatment of autoimmune diseases including rheumatoid arthritis, psoriasis, and Crohn's disease, which require once-weekly use.

Overdose of methotrexate can lead to serious adverse effects such as haematopoietic disorders (leukopenia, thrombocytopenia, anaemia, and pancytopenia) and gastrointestinal reactions (mucositis, stomatitis, oral ulceration, gastrointestinal ulceration, and gastrointestinal bleeding). Some reports of overdose have been fatal. In these fatal cases, events such as sepsis or septic shock, renal failure, and aplastic anaemia were reported.
The NPSA (2006) Patient Safety Alert highlighted very occasional problems with taking methotrexate causing harm and even death.

However, since 1 Jan 2006 and up to 30 July 2020, there have been 11 Yellow Card reports of serious toxicity associated with inadvertent daily dosing of once-weekly methotrexate in the UK. Medication errors that lead to taking more than the intended dose (including daily instead of once-weekly dosing) have been identified at all steps in the treatment pathway, including prescribing and dispensing of methotrexate, transfer of care (for example, hospital admission and discharge) and communicating with patients.

MHRA (Sept 2020) produced a Drug Safety Update: Methotrexate once-weekly for autoimmune diseases: new measures to reduce risk of fatal overdose due to inadvertent daily instead of weekly dosing .

To ensure the safe use of methotrexate, ensure your organisation is compliant with the recommendations made in the Patient Safety Alert and the Drug Safety Update.

The Pan Mersey Area Prescribing Committee recommends

- Methotrexate should only be prescribed by healthcare professionals who are fully aware of the benefits and risks of treatment and who have all necessary prescribing competence.
- All specialities, including haematology, should prescribe oral methotrexate dose in multiples of **2.5 mg** tablets and the total dose in milligrams must also be included.
  For example, "Three 2.5 mg tablets (7.5 milligrams)"
- Methotrexate 10mg tablets **must not** be prescribed or supplied.
- When oral methotrexate is prescribed as a once weekly dose the prescription and the dispensing label must clearly show the dose in milligram and the number of tablets to be taken and the frequency as "**once a week on…"** (*The day of the week should be specified in full*).
- Prescribing of methotrexate with co-trimoxazole or trimethoprim should be avoided and **should not** occur under any circumstances [†] . This also applies to people that have recently taken methotrexate.

All Prescribers

Oral

- Prescribe oral methotrexate dose in multiples of 2.5 mg tablets and the frequency as "**once a week on…"** (*The day of the week should be specified in full*). The total dose in quantity of tablets and milligrams must be included.
- 10 mg tablets **must not** be prescribed or dispensed.

Subcutaneous

- Injectable methotrexate must be prescribed as PRE-FILLED syringes or pens only.
- Subcutaneous methotrexate must be prescribed by brand and include the generic name where prescribing systems allow. Primary care must be informed of any brand switch of subcutaneous methotrexate.
- If switching between subcutaneous methotrexate products is necessary, patients should be informed in advance. For patients who are self-administrating training must be provided to ensure that new brand is administered correctly.

On initiation of treatment with methotrexate

- The patient must be carefully advised of the dose and frequency and the reason for taking methotrexate and any other prescribed medicine (e.g., folic acid).
- Monitoring requirements should be discussed with the patient and details recorded in the patient's notes.
- When prescribing methotrexate as a once weekly oral formulation, healthcare professionals should take into consideration a patient's overall polypharmacy burden and ensure that the patient is able to understand and comply with once-weekly dosing.
- Provide the patient/carer with full and clear dosing instructions on the once weekly dosing and decide together with the patient/carer on which day of the week the patient uses methotrexate. The day of the week agreed should be noted down in full in the patient's records.
- Inform patients of the potentially fatal risks associated with taking methotrexate more frequently than prescribed, and specifically, that it should not be taken daily.
- All patients should be provided with a hand-held information booklet or local equivalent. Instruct patients to use the booklet to alert any healthcare professionals they consult who are not familiar with their methotrexate treatment, about their once-weekly dosing schedule (for example, on hospital admission, change of care).
- The patient must be warned to report immediately the onset of any features of blood disorders (e.g., sore throat, bruising, and mouth ulcers), liver toxicity (e.g., nausea, vomiting, abdominal discomfort, and dark urine), and respiratory effects (e.g., shortness of breath, stomatitis).

Safety

- Prescribing of methotrexate with co-trimoxazole or trimethoprim should be avoided and **should not** occur under any circumstances [†] . This also applies to people that have recently taken methotrexate.
- There are other potentially significant drug interactions with methotrexate, therefore prescribers must familiarise themselves with the patient's medication history when prescribing methotrexate and ensure there are no clinically significant drug interactions.
- Methotrexate therapy should be reviewed, and temporary suspension considered when patients are being treated for active infection. The specialist team responsible for methotrexate therapy will advise on ongoing

[†] In exceptional circumstances, specialist paediatric services may use co-trimoxazole prophylaxis, with watchful increased monitoring, for Pneumocystis pneumonia in children on immunosuppressive triple therapy that includes low dose methotrexate for inflammatory bowel disease or for leukaemia patients on maintenance methotrexate treatment. The specialist paediatric service will prescribe, supply, and monitor treatment.

suspension and the decision to resume therapy. Inform the patient of any suspension of therapy and clearly communicate when to resume or who will make the decision to resume therapy.

Secondary Care Prescribers

- It is the prescriber's responsibility to record the correct dosage and frequency (including day) on the hospital drug administration chart and to strike out the six days of the week when a dose must not be administered.
- For electronic prescribing systems, prescribers need to ensure a once weekly prescription (on the appropriate day) is selected. Electronic prescribing systems should be configured with suitable alerts to remind prescribers of the weekly requirements.
- Ensure that methotrexate is recorded in the patient's medication record (e.g., summary care record or discharge summary) including day of the week administered.

Primary Care Prescribers

- If prescribing and monitoring are to be carried out by primary care, prescribers must ensure a shared care agreement is in place and details are recorded in the patient's records.
- At the issue of each prescription ask to see the patient's monitoring booklet and check if any dose changes have been made since the last prescription issue.
- If oral or subcutaneous methotrexate is being issued by the hospital, primary care prescribers must ensure that it is recorded on current medication record as a "Medicine Prescribed Elsewhere" or "Hospital Drug".

Dispensing Pharmacy in Primary Care

- Ask to see the patient's monitoring booklet and check if any dose changes have been made since the last prescription issue.
- Always check for drug interactions. If a drug interaction is identified, ensure prescriber is made aware before dispensing.
- Pharmacists should refuse to dispense and query any prescription for 10 mg tablets with the prescriber.
- On dispensing, the pharmacist should ensure the defined day of the week is clearly displayed on the dispensing label and on the outer packaging.
- Check carefully at every new prescription /dispensing that the patient/carer understands that the medicine must be used once weekly, and that overdose can lead to serious side effects.
- Inform the patient/carer of signs of overdose and instruct them to promptly seek medical advice if they think they have taken too much methotrexate.
- Oral methotrexate products with indications requiring once-weekly dosing come with a Patient Card (July 2020), which will prompt patients to take methotrexate once a week and to record the day of the week for intake. It will also help patients to identify the signs and symptoms of overdose. On dispensing, the pharmacist should transcribe the defined day of the week onto the card. The pharmacist should demonstrate the Patient Card to the patient/carer and instruct them to carry the card with them in their purse or wallet and to use it to alert any healthcare professionals they consult about their once-weekly dosing schedule (for example, on hospital admission, change of care).

All Healthcare Professionals

- Be aware of patients who present with symptoms such as sore throat, mouth ulcers, breathlessness, dry persistent cough, vomiting or diarrhoea, stomatitis as these can be signs of oral methotrexate toxicity or intolerance.
- Suspected adverse reactions **and any medication error** which results in patient harm should be reported to the MHRA through the Yellow Card Scheme via MHRA Yellow Card scheme.
- Educational materials (July 2020) for healthcare professionals is available for oral products with indications requiring once-weekly dosing. These materials should be used in conjunction with local guidance materials if available.

References

1. The National Patient Safety Agency. Improving compliance with oral methotrexate guidelines. NPSA/2006/13. June 2006
2. NPSA: Towards the safer use of Methotrexate NPSA 2004
3. MHRA Drug Safety Update: Methotrexate once-weekly for autoimmune diseases: new measures to reduce risk of fatal overdose due to inadvertent daily instead of weekly dosing. Sept 2020