

Guidance for Pharmacists on Safe Supply of Oral Methotrexate

1. Introduction

Methotrexate is a potent immunosuppressant used in the treatment of active rheumatoid arthritis in adults, severe recalcitrant psoriasis and some oncological indications.

Oral methotrexate for rheumatological and dermatological indications is administered on a once-weekly basis.

Incorrect dispensing, prescribing and use of methotrexate can result in significant patient morbidity and mortality, due to severe adverse effects which can occur abruptly. Such cases have been reported in Ireland and elsewhere and are of concern to all individuals involved in the supply of methotrexate.

These cases have primarily related to overdosage with oral methotrexate, where errors occurred in the prescribing, dispensing or use of the drug, most commonly where the drug was taken daily rather than weekly. Other cases of patient harm have resulted from confusion between the different strengths of oral methotrexate tablets; cases of deliberate overdosage have also been reported.

Errors in dosing may, in some cases, have been compounded by a lack of monitoring for recognised side-effects and symptoms of toxicity. (See signs of methotrexate toxicity detailed below)

Pharmacists play a critical role in ensuring the safe use of methotrexate, through their participation in the educating, counselling and monitoring of patients.

Key Messages
➤ It is essential to ensure that patients/carers are aware of the once weekly nature of the methotrexate dose and that this message is reinforced regularly in patient counselling.
➤ Patients/carers need to be clear about the number of tablets they take each week and pharmacists should be aware that the usual dose range is 7.5mg-25mg orally once weekly.
➤ It is essential that patients/carers are aware of the signs and symptoms of methotrexate toxicity. Patients and their carers need to be aware of the importance of identifying these signs as early as possible and urgently seeking medical assistance if they suspect they have these symptoms.
➤ The supervising pharmacist or other designated pharmacist is responsible for the management, supply and patient/carer counselling for methotrexate.
➤ Only the 2.5mg strength tablets are dispensed and patients are actively encouraged and supported in taking one strength only, irrespective of dose.
➤ Methotrexate should be stored in the dispensary in a manner which will trigger additional safety considerations.
➤ All medicine/healthcare queries, irrespective of the nature of the query, from methotrexate patients or their carers, must be referred to the pharmacist for review and intervention.
➤ Particular care and input is required from the pharmacist when a patient is initiated on methotrexate, when a new methotrexate patient/their carer presents to the particular pharmacy, when there is a change of dosage or a change in prescriber.
➤ Additional consideration must be given to the counselling and monitoring needs of patients on methotrexate in residential care settings e.g. nursing homes.
➤ It is recommended that methotrexate is dispensed in separate, clearly labelled, weekly allocations.
➤ Liaison with the prescriber to prevent any discrepancies in pharmacist and prescriber advice will promote patient safety and adherence.

Possible Signs of Methotrexate Toxicity - warranting immediate reporting and referral	
Features of Blood disorders	Sore Throat/Other Infections*
	Fever/Chills*
	Mouth Ulceration
	Easy bruising or bleeding
Liver Toxicity	Diarrhoea
	Vomiting
	Unexplained Rash
Respiratory Effects	Breathlessness
	Dry persistent cough

*Signs of Neutropenia, high risk of patient mortality/morbidity

2. Guidance for supply of methotrexate by a pharmacist:

Patient Review

- For each and every dispensing of methotrexate, the pharmacist must personally carry out a complete **review** of the patient's previous dispensed medication history (consider a specific alert on PMR to highlight patients taking methotrexate).
- This review must include an assessment of the time period since last dispensing, a thorough **interactions** check and a review of the use of non-prescription or herbal medicines. Relevant information should be noted on the PMR.
- It is essential to assess the patient for the occurrence of any side effects which warrant referral, particularly sore throat or other signs of infection, since the last supply of methotrexate. (See signs of methotrexate toxicity detailed above)
- It is essential to regularly ascertain the patient's awareness of the necessity for regular **blood monitoring**.
- Particular care must be taken when there is any **change of medication**, either to methotrexate or other medicines, to ensure that the patient, or patient's representative, clearly understands the adjustments.

Dispensing

- The **dose** should lie in the usual dose range 7.5mg-25mg orally once weekly: any deviation from this, or the absence of an actual dosage instruction on the prescription, should be directly confirmed/ queried with the prescriber.
- If the dosage on a prescription states a once daily dose, the pharmacist must always query with the prescriber whether this is correct.
- When a prescription is issued the pharmacist should always confirm the indication for prescribing, particularly when a prescription is issued by a non-hospital based prescriber.
- The pharmacist should be familiar with the Summary of Product Characteristics for the methotrexate product(s) being supplied, and refer to same when necessary, accessible at www.imb.ie or www.medicines.ie
- Gloves should always be used in the handling of methotrexate tablets outside of their packaging.
- The **labelling** must be,
 - Clear and legible, using type face which is of an appropriate size to ensure that the directions are clear. "As Directed" is never a suitable term to use to instruct a patient as to how the medicine is to be taken.
 - The medicine should be labelled appropriately to cater to the individual needs of the patient.
 - It is recommended that the dose be stated on the label in number of tablets, total dose, weekly interval and day of the week on which it is to be taken i.e. Take **six** x 2.5mg tablets (15mg in total) **once a week** on a **Friday**.
- The pharmacist should be aware that prescribers are also being encouraged to specify the day of intake on the prescription as highlighted in the 47th edition of the IMB Drug Safety Newsletter, outlining the outcome of the EU review of the issue, and to ensure that pharmacy labelling is consistent with the prescription.

- Extra caution should be taken to clarify the precise dosing instructions where a consultant/hospital prescription has been transcribed, for example on to a GMS prescription form.
- Only in exceptional circumstances should more than a month's supply of methotrexate be dispensed, at one time.
- It is recommended that in the dispensing of a month's supply of methotrexate, where appropriate for the individual patient, the medicine be divided into individual, clearly labelled, **weekly allocations**, to aid compliance and reduce confusion.
- As manual dexterity may be a problem for some patients, an individual consultation/assessment relating to this is necessary, to ensure that they can easily open the packaging and therefore that the tablets will not be transferred to an alternative, possibly inadequately labelled, container.
- It is recommended that the strength and quantity of the medication are always **double checked** before delivery to the patient.
- It is important to furnish the patient with the product's patient information leaflet/ package leaflet at each dispensing, this may require the package leaflet being copied in the case of broken bulk dispensing, in accordance with current PSI guidance.
- If folic acid is also dispensed at the same time, it should be ensured that the patient can differentiate between the methotrexate and folic acid, is completely clear on the dosage regimen of this medication and appropriate clear labelling is used.
- **Patients who have previously been using 10mg strength tablets need to be carefully and sensitively advised about switching to the use of 2.5mg tablets only.**
 - Challenges for some patients in changing from 10mg to 2.5mg strength tablet are acknowledged.
 - Prescribers should be informed of the pharmacy's policy with regard to using only 2.5mg strength tablets.
 - All changes should be discussed in advance with the prescriber.
 - In cases where the patient objects or is apprehensive regarding the change, liaison with the prescriber is especially important in assuring patient safety and adherence, and preventing any discrepancies in pharmacist and prescriber advice.
 - It is important to take into account that patients/carers may be more aware of the number of tablets they take, rather than the strength of tablets.

Patient Counselling and Monitoring

- The **pharmacist must personally deliver** the appropriately labelled medicine to the patient/carer, and must **verbally confirm** the dosage requirements with the patient, reinforcing the labelled instructions in a clear manner. This understanding must be confirmed demonstrably by the patient/carer.
- An offer must be made to counsel the patient every time the patient receives methotrexate, specifically discussing the importance of adhering to the correct dose and frequency, and patient awareness of side-effects/symptoms which require immediate reporting to their doctor or pharmacist (see signs of toxicity information detailed above).
- The patient/carer should be made aware of and offered the facility of the pharmacy's patient consultation area for any counselling or discussion.
- A patient information notice, to remind the patient of these key safety issues may be helpful to provide. (see template below)
- The pharmacist should highlight the importance of **safe storage** to the patient in order to reduce the risk of inadvertent poisoning.
- Emphasize with the patient the importance of **notification to other health care professionals** that they are taking methotrexate.
- Any patient presenting at a pharmacy who is known to be taking methotrexate, or indicates that they are taking the drug, should be seen by the pharmacist, irrespective of the nature of the advice being sought.
- Any adverse drug reactions suspected to be related to methotrexate should be notified to the Irish Medicines Board in the usual way, including those resulting in harm to patients associated with medication errors.

3. Professional management and medication safety considerations

Within each pharmacy the superintendent and supervising pharmacists must ensure the medication safety issues for methotrexate are considered and addressed by appropriate clinical governance measures. It is therefore important that clear documented policies and procedures are in place which address relevant patient safety and risk management issues, to ensure consistent practice in the management of methotrexate.

All pharmacists and other staff must be aware of the need for extra vigilance around the supply and use of methotrexate, in particular the importance of weekly dosing and of awareness of symptoms of overdosage or toxicity.

The methotrexate policy and procedure(s) should be reviewed and updated regularly in accordance with best professional practice, annually at a minimum or if further new information or guidance emerges.

Patient Information Template-

Using Your Methotrexate Safely

- Your methotrexate medicine should only be taken ONCE WEEKLY, on the same day each week.
- As you are taking methotrexate, there is a risk that this medicine can sometimes cause serious adverse effects that need immediate attention from your doctor.
- The following is a list of SOME of the signs/symptoms that you should tell your doctor or pharmacist about IMMEDIATELY.

Warning signs and symptoms
Sore Throat/Other Infections
Fever/Chills
Mouth Ulceration
Easy bruising or bleeding
Diarrhoea
Vomiting
Unexplained Rash
Breathlessness
Dry persistent cough

- If you have any questions about methotrexate or any other medicine you are taking, please ask your pharmacist. They will be happy to help you.