Guidance for Improving the Safe Use of Oral Methotrexate in Primary Care

Information for GPs and Community Pharmacists

CONTENTS

Guidance for Improving the Safe Use of Oral Methotrexate in Primary Care

1. Introduction

Following reports of a number of patient safety incidents involving oral methotrexate, the NPSA issued an alert which outlines the actions for NHS organizations to reduce the risks associated with this drug. http://www.nrls.npsa.nhs.uk/resources/?entryid45=59800. In 2005, the Department of Health Social Services and Public Safety (DHSSPS) Circular HSS (MD) 22/2005 also highlighted good practice to minimise the risk of future serious incidents relating to methotrexate http://www.dhsspsni.gov.uk/hssmd22-05.pdf.

Methotrexate is available as oral tablets, liquid and an injectable form. Oral methotrexate is widely prescribed for its clinical benefit in the treatment of rheumatoid arthritis and severe psoriasis. It is administered ONCE A WEEK for these conditions (maximum dose is usually 20-25mg).
Medication incidents have occurred with oral methotrexate because:

- Weekly doses have been taken on a daily basis
- 10mg tablets have been confused with 2.5mg tablets
- Higher doses for malignant conditions have been confused with doses for non-malignant conditions
- 'Monday' has been misread as 'morning'

This guidance document outlines good practice for primary care to minimise the risk of serious adverse incidents relating to methotrexate. It should be noted that this guidance is relevant to prescribing for all non-malignant conditions. The use of methotrexate for other conditions with a different dosing regimen must be considered separately.

2. Prescribing Guidance

2.1 Methotrexate Register

- Methotrexate is an amber-listed drug. Prescribing in primary care should occur only when shared- care arrangements have been agreed between the GP and specialist http://www.ipnsm.hscni.net/
- The practice should have a system in place for managing patients receiving oral methotrexate including prescribing responsibilities , monitoring of patients bloods and dose changes
- An up-to-date register of patients receiving methotrexate should be maintained. This should clarify responsibilities for prescribing, monitoring and review
- All patient records (paper and electronic) should include a flag or visible prompt that the patient is receiving oral methotrexate and should clearly document the indication for use of methotrexate.

2.2 Strengths of preparation, dose and directions

(a) Strengths

- Methotrexate tablets should be prescribed as 2.5mg tablets only

- Methotrexate liquid should be prescribed as 10mg/5ml only

Prescriptions for all other strengths must be queried directly with the prescriber/specialist

Note: Prompts to remind prescribers of the recommended strengths are possible with some clinical systems. For advice, speak to your IT system provider.

(b) Dose and directions

- The prescription direction should be precise and must include 'Take ONCE A WEEK ON A specific day of the week (not MONDAY so as to avoid being misread as morning)
- Prescription instructions must state both the dose and the number of tablets to be taken i.e. 10mg (four x 2.5mg tablets)
- "As directed" is not acceptable. Community pharmacists have been advised to query prescriptions for oral methotrexate without specific directions.

2.3 Folic Acid

- Folic acid may reduce the risk of gastrointestinal and haematological toxicity associated with methotrexate. Patients taking methotrexate should be prescribed folic acid 5mg once weekly. This should be taken one or two days after the methotrexate.

2.4 Regular Monitoring

- Systems should be in place to ensure regular monitoring is carried out in accordance with the oral methotrexate shared-care guideline and to check that it is safe to continue treatment http://www.ipnsm.hscni.net/.

2.5 Staff training

- Staff training on acute and repeat prescribing should be an integral part of staff induction. All relevant staff, including locums, should be made aware of the practice protocol for issuing prescriptions for methotrexate as part of this training.

2.6 Reauthorisation of prescriptions

- Consideration needs to be given to the duration of supply and frequency of issue of repeat prescriptions for methotrexate. **Ideally patients should not be given more than a four week supply**
- Systems should be in place to highlight at any one time a patient who appears to be ordering methotrexate at a higher or lower than intended frequency. Potential compliance issues should always be flagged to the GP/prescriber
- A check should be carried out to ensure necessary monitoring is conducted prior to issuing or reauthorising repeat prescriptions. Refer to shared care guideline http://www.ipnsm.hscni.net/
- Reception staff should not have the authority to reissue or reauthorise methotrexate prescriptions
- If methotrexate has been prescribed previously as an acute item, some clinical systems allow this to be “copied” at a later date to save re-typing. This practice is strongly discouraged as dose /directions may have changed.

2.7 Signing of prescriptions

- Repeat prescriptions for oral methotrexate should be separated from other repeat prescriptions and retained for the prescriber to review prior to signing

2.8 Patient Information

- There should be a record in the patient’s notes of education given to them about oral methotrexate including signs of toxicity. Information on the risks and benefits of oral methotrexate should be provided to the patient or their carer. Confirmation of understanding and consent to methotrexate treatment should be recorded.

- The methotrexate monitoring schedule should be explained and patient-held monitoring booklet issued. It is recommended that patients retain their monitoring/record book and that all results and/or dose changes are documented here. One such document is the patient-held National Patient Safety Alert (NPSA) methotrexate treatment blood monitoring and dosage record bookletand is available from the Business Service Organisation (BSO). This booklet which contains important patient information regarding methotrexate has an additional safety label attached highlighting that only methotrexate 2.5mg tablets (or in exceptional cases, 10mg/5ml liquid), should be used in Northern Ireland. To order copies of the booklet, please phone the stationery helpline: 028 9053 5652 and leave the GP surgery full address and postcode.

2.9 Ensuring an Accurate Patient Record

- The patient record (both paper and electronic) should be kept up to date to ensure the correct information is used in future prescriptions and that the correct information is communicated to secondary care e.g. on admission to hospital
- If paper and electronic systems are used in tandem, it is essential that alterations to the prescribing of oral methotrexate are documented in BOTH locations. For this reason, it is strongly recommended that only one system is kept
- If an incorrect dose, formulation or frequency has been entered in an electronic prescribing record this should be annotated that an incorrect dose, formulation or frequency had been erroneously entered along with the date of the incorrect entry. If an erroneous record is not corrected, the incorrect information may be used in future dispensing.
- Records may need to be updated following a query from a Community Pharmacist or other health care professional
- If methotrexate is stopped, it should be promptly removed from the prescribing record to ensure there is no possibility of it being reissued. The reason for stopping treatment should be clearly documented in the patient's record
- Only a GP should add, or make amendments to, methotrexate in the patient's record.

2.10 Hospital Admission and Discharge

(a) Admission

Written information accompanying patients from primary care to secondary care should provide the following details in relation to Methotrexate:

- dose
- frequency
- formulation i.e. tablets or liquid
- day of the week when methotrexate is to be taken
- indication
- date started
- intended duration of treatment

As this is not always possible e.g. out of hours, the NPSA booklet or a patient held monitoring card, will assist with providing up-to-date prescribing information.

(b) Discharge

Methotrexate prescribing in primary care should occur only when shared- care arrangements have been agreed between GP and specialist. When a hospital specialist is initiating or altering the dose of oral methotrexate, the GP should be provided with clear details of

- dose
- frequency
- formulation i.e. tablets or liquid
- day of the week when methotrexate is to be taken
- indication
- date started
- intended duration of treatment

If this information is not provided or is illegible / unclear, the specialist should be contacted for clarification before the prescription is issued.

(c) Shared Care Guidelines (SCGs)

- Regional SCGs are available for prescribing methotrexate in non-malignant conditions. Prescribers should be familiar with this guidance and their responsibilities (available at www.ipnsm.hscni.net) Methotrexate monitoring requirements are specific to each indication for use.
- Systems should be in place to ensure monitoring is carried out in accordance with the SCGs. If patients do not attend for regular blood monitoring as agreed in the SCG, continued prescribing may not be appropriate and should be discussed with the patient, hospital specialist and community pharmacist as needed.
- All blood monitoring results should be checked by the prescriber and appropriate action taken where necessary.

2.11 Community Pharmacy Issues

The Community Pharmacist has a professional responsibility to ensure:

- It is safe to dispense a prescription for oral methotrexate
- All prescriptions for methotrexate are clear and complete
- Prescriptions for 10mg tablets (or any other issues relating to methotrexate) are queried directly with the prescriber, rather than with non-medical staff, and a note of the query made on the prescription
- Directions are clarified if the dose prescribed is not written as 'Take once a week'
- Interactions are highlighted to the prescriber.

See section 3 for full details of Community Pharmacy recommendations..

.

2.12 Warning Signs and Symptoms

Healthcare staff should be trained to recognise the signs and symptoms of methotrexate toxicity or intolerance. These can be misinterpreted, for example, as infection rather than methotrexate toxicity.

- Signs of methotrexate toxicity include nausea, decreased resistance to infection (especially respiratory, urinary tract or shingles/chickenpox) alopecia, rash, stomatitis, diarrhoea
- Patients should be asked about oral ulceration/sore throat, unexplained rash or unusual bruising at every consultation
- Patients who take methotrexate and ask for advice on minor infections, especially sore throat, should be referred to the GP for advice
- Patients complaining of unexplained dry cough should be referred immediately to the hospital specialist
- Nurses providing triage in the practice should consider methotrexate toxicity during all consultations
- Prescribers should be aware of common drug interactions with methotrexate e.g. do not prescribe concomitantly with:
    - Trimethoprim or co-trimoxazole due to risk of pancytopenia
    - Drugs with potential hepatotoxic or nephrotoxic effects

  (Refer to BNF (Appendix 1) for a full list of drug interactions with methotrexate)

2.13 Immunisations

- Patients should receive the influenza vaccine annually unless otherwise advised by the initiating specialist
- Patients should have had ONE DOSE of pneumococcal vaccine. See BNF or Green Book
- Passive immunisation using Varicella immunoglobulin (VZIG) should be considered in non immune patients if exposed to chickenpox or shingles. Contact Virology Department Royal Group of Hospitals for advice if exposure is suspected
- **Note**: Live vaccines should be avoided, except on the advice of the initiating specialist.

2.14 Kardexes for Patients in Care Homes

Information on Kardexes must be up-to-date and accurate. Relevant care home staff should be aware of procedures for the safe handling, recording and administration of methotrexate.

2.15 Medication Incidents

If a medication incident, or a 'near miss' involving oral methotrexate has occurred, the practitioner discovering the medication incident should ensure that the incident is communicated to other colleagues involved in the care of the affected patient. The incident should be reported to a member of the HSCB Medicines Governance Team to allow learning from the incident to be shared with a view to preventing further similar incidents. The AIF1 form which is available on the primary care intranet site http://primarycare.hscni.net should be used.

Prescribers should note that a regional audit has also been developed for GP practices to audit their prescribing of methotrexate. This is available at http://primarycare.hscni.net/pdf/MTX_GP_audit_final_May_09 .

3. Dispensing Guidance

3.1 Introduction

- This guidance aims to address the DHSSPS recommendations and outlines good practice, to ensure that dispensing of methotrexate accurately reflects the prescriber's intentions and is consistent with the needs and safety of the patient.
- Methotrexate is a cytotoxic drug and as such must have a designated storage and dispensing area within the dispensary.

GPs have been given recommendations on prescribing which include:

- **2.5mg tablets only** should be prescribed and liquid should only be prescribed as the **10mg/5ml** strength

- The prescription direction should be precise and should state '**ONCE A WEEK ON A'** specific day of the week, not MONDAY so as to avoid being misread as mane

- Prescription instructions must state both the dose and the number of tablets to be taken i.e. 10mg (four x 2.5mg tablets)

See Section 2 for more details of GP recommendations.

3.2 Standard Operating Procedures (SOPs)

All pharmacies should have a Standard Operating Procedure for dispensing oral methotrexate irrespective of the number of methotrexate patients seen. These pharmacy-specific written procedures must detail what should be done, when, where and by whom and should be available for all staff involved in the dispensing process including locums. The following guidance is written to reflect the order of events within a Standard Operating Procedure as recommended by the Pharmaceutical Society of Northern Ireland.

3.3 (a) Assessment of the prescription for validity, safety and clinical appropriateness

(i) Assessment of the Prescription Form

Assessment should include new prescriptions and prescriptions for existing methotrexate patients

- Tablets should only be prescribed as the 2.5mg strength or the liquid should only be prescribed as 10mg/5ml strength
- Prescriptions for 10mg tablets or other strengths of liquid must be queried with the prescriber and queries noted on prescriptions and the PMR
- The directions must include 'Take ONCE A WEEK ON A' specific day of the week, not MONDAY so as to avoid this being misread as mane or morning
- Directions must be clarified if the prescription states a daily dose
- Prescription instructions must state both the dose and the number of tablets to be taken i.e. a dose of 10mg should be written as four tablets x 2.5mg tablets
- An absence of directions or 'As directed' is unacceptable as a dosage instruction for oral methotrexate. A specific dose should always be stated on oral methotrexate prescriptions.
- Oral methotrexate should not be dispensed solely from an 'owing' as a mistake may have been made in generating the 'owing' record, or from a verbal request. The original prescription should always be referred to.
- Refer to Appendix 1 of the BNF for information on drug interactions with methotrexate
- The patient's monitoring booklet should be checked to ensure there have been no recent dose changes and that monitoring has been carried out.

(ii) Assessment of the Patient Medication Record (PMR)

- A record of the exact dose should be kept in the PMR
- If an incorrect dose, strength, formulation or frequency has been entered in the PMR system, it should be annotated that an incorrect dose strength, formulation or frequency had been erroneously entered along with the date of the incorrect entry. If an erroneous record is not corrected, the incorrect information may be used in future dispensing.
- If the PMR indicates that a patient is taking their methotrexate at a greater or less than intended frequency, this should be discussed with the patient and/or GP.

(b) Interventions and problem solving

- Queries concerning oral methotrexate should be addressed **directly with the prescriber** rather than non-medical staff
- A note of the query should be made on the prescription and in the PMR
- If the details on the prescription are incorrect, the GP should be advised to ensure the practice electronic record is updated to ensure future prescriptions

contain the correct information and do not lead to the re-issue of an incorrect prescription.

(c) Assembly and labeling of required medicine

(i) Methotrexate 2.5mg Tablets

- Only 2.5mg tablets should be supplied
- When purchasing oral methotrexate tablets and folic acid tablets, the pharmacist should ensure that these medicines can be easily differentiated by healthcare staff and patients e.g. purchase blister packs of tablets rather than "loose" tablets
- In addition, oral methotrexate packaging should carry the warning '*Check dose and frequency – methotrexate is usually taken once a week'.*

If methotrexate 10mg tablets are required in exceptional circumstances e.g. risk assessed compliance issues and confirmation of this has been obtained from the prescriber, they should be stored separately from the 2.5mg tablets in a segregated area to avoid picking/dispensing errors.

(ii) Methotrexate 10mg/5ml Liquid

- As methotrexate liquid is a 'special' it may not be available to order by community pharmacists through the usual wholesalers. Supplies may be ordered from the normal community pharmacy wholesaler but methotrexate liquid must be ordered as 10mg/5ml. The SCG suggests Nova Laboratories but this is not the only company that manufactures this product.
- Counselling should be provided for the patient regarding the handling and disposal of oral methotrexate. This should be supplemented by written information. For liquid oral methotrexate, information should also be provided for dealing with spillage. Cannon Hygiene provide a collection and disposal service for cytotoxic drugs, including methotrexate.

(d) Accuracy checking procedures

- Checking procedures should ensure that only methotrexate 2.5mg tablets or methotrexate 10mg/5ml liquid has been dispensed and that the label includes direction to take 'ONCE WEEKLY ON A' specific day of the week, not MONDAY

(e) Transfer of medicine to the patient

- Community pharmacists should give advice consistent with that provided by the GP, consultant or hospital pharmacist
- Advice should highlight the importance of weekly dosing rather than daily dosing and the use of 2.5mg tablets or 10mg/5ml liquid

- Assess the needs of the individual patient e.g. manual dexterity may be an issue for some patients so ensure that the medication can be accessed easily
- It is good practice to discuss dose changes with the patient and/or carers and to assess their understanding of them
- Show the patient how to differentiate between the oral methotrexate and folic acid products. If they take both medicines at the same time, they will need to know how to distinguish between them, given that both may be round yellow tablets of similar size.
- Ask the patient if they have experienced any side effects and what the side effect was. Check if they have spoken to the prescriber about this side effect and what the prescriber told them to do. If they have not spoken to the prescriber refer them back to the prescriber. Patients who have been on methotrexate long term may be at risk of pulmonary fibrosis and present with symptoms such as breathlessness, dry persistent cough. Intolerance may present as diarrhoea or vomiting. You may need to refer them back to the prescriber.
- Prior to dispensing, pharmacists should ask to see the patient's monitoring booklet and check the drug dose and the blood tests. If any dose changes have been made since the last prescription, check this matches the current prescription. Check that the monthly bloods have been done, if not refer the patient back to the prescriber. Booklets are usually supplied by the initiating consultant. One such booklet is the patient-held NPSA methotrexate treatment blood monitoring and dosage record booklet. This is available from the Business Service Organisation with an additional safety label attached. To order copies of the booklet, please phone the stationery helpline: 028 9053 5652 and leave the pharmacy contractor number.
  However, it should be noted that patients are usually supplied with the booklet by the initiating consultant.

3.4 Emergency Supplies

As with all emergency supplies at the request of the patient, each request must be treated on its merits. Pharmacists must be satisfied that the patient is still receiving this treatment, and that there is an immediate need and it is impractical to get a prescription straight away. Pharmacists should apply caution to emergency requests for methotrexate to ensure the correct dose is supplied.

If the patient requires methotrexate 10mg/5ml liquid and it is not stocked, it may be necessary to liaise with hospital pharmacy colleagues to obtain a timely supply.

3.5 Warning Signs and Symptoms

Healthcare staff should be trained to recognise the signs and symptoms of methotrexate toxicity or intolerance. These signs and symptoms may be misinterpreted as suggestive of, for example, infection rather than methotrexate toxicity.

- Adverse effects include: nausea, decreased resistance to infection (especially respiratory, urinary tract or shingles/chickenpox, alopecia, rash, stomatitis, diarrhoea)
- Respiratory function: patients complaining of unexplained dry cough should be referred immediately to the GP
- Patients who take methotrexate and ask for advice on minor infections, especially sore throat, should be referred to their GP
- Methotrexate interacts with some common OTC medicines such as aspirin and ibuprofen. Pharmacists should ensure patients are appropriately questioned and advised when purchasing OTC medicines or obtaining medicines through the Minor Ailments Service.

3.6 Medication Incidents

If a medication incident, or a 'near miss', involving oral methotrexate has occurred, the practitioner discovering the medication incident should ensure that the incident is shared with other colleagues involved in the care of the affected patient. It should also be reported to a member of the HSCB Medicines Governance Team using the AIF1 (pharmacy anon) form
http://www.hscboard.hscni.net/medicinesmanagement/Medicines%20Governance/index.html#P-1_0
This will allow learning from the incident to be shared with a view to preventing further similar incidents

3.7 Medication Administration Records (MAR)

Pharmacists who supply printed MAR charts along with medicines to the residents of care homes must ensure the information on the MAR is up-to-date and accurate. This is particularly important for drugs which may interact or are contraindicated with methotrexate.