Guide for Healthcare Professionals
Measures to avoid potentially fatal dosing errors with methotrexate for inflammatory diseases

Methotrexate 2.5 mg film-coated tablets

Methotrexate 2.5 mg film-coated tablets has been approved in Malta for two different group of indications, each with a different dossing schedule:

In inflammatory diseases *(once weekly dosing)*

- Severe, active, classical or definite rheumatoid arthritis.
- Severe, uncontrolled psoriasis.

In oncology *(daily dosing)*

- Acute leukaemias.
- Non-Hodgkin's lymphoma.
- Soft-tissue and osteogenic sarcomas.
- Solid tumours, particularly, breast, lung, head and neck, bladder, cervical, ovarian and testicular carcinoma.

This Guide is not a substitute for Remedica's Methotrexate Summary of Product Characteristics (SmPC). Please consult the SmPC for full prescribing information.

NOTE: Important warning about the dosage of Methotrexate

In the treatment of rheumatoid arthritis and psoriasis, Methotrexate **must only be taken once a week.** Dosage errors in the use of Methotrexate can result in serious adverse reactions, including death.

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1. Purpose of this guide

This Guide has been prepared for healthcare professionals who prescribe, dispense or work with patients who use Methotrexate and is intended to ensure that the medicine is used correctly. This Guide is not a substitute for Remedica's Methotrexate Summary of Product Characteristics (SmPC); please consult the SmPC for full prescribing information.

The main objective of this guide is to take measures to avoid potentially fatal dosing errors with methotrexate for inflammatory diseases. It is recognized that medication errors can sometimes happen despite appropriate prescribing and patient/carer instruction and so this guide also describes the risks and what to do in the event of a medication error.

Extensive assessment of spontaneously reported post-marketing cases has been performed by the PRAC and although some relevant data might not have been provided in all spontaneously reported post-marketing cases, the root cause analysis was further substantiated by the assessment of literature data, which provided more detailed description of methotrexate medication error cases. The feedback received from healthcare professional organisations also provided further insight on the root causes for errors.

Based on the available data, the PRAC noted that the above mentioned risk of medication errors can occur at all stages of the medication process, from prescription to administration. Different reasons for the occurrence of medication error have been identified. The ambiguity due to the product being authorised in different indications with different dosing schedules and lacking clear and visible warnings alerting on the once weekly dosing schedule on the packaging and the use of bulk packaging were identified as root causes for medication errors. Lack of knowledge and clarity on the weekly dosing schedule in some indications was also recurring feature and not limited to patient level. Admission to hospital and transfer of care between institutions and physicians was also noted as a root cause due to poor or a lack of communication between patient/physician, physician/physician, physician/nurse. Dispensing errors have also been reported. The case report analyses showed that the elderly patient population was more predisposed for inadvertent daily use of methotrexate, with more than half of the cases reporting elderly population (65 or over). Other subgroups of patients were also identified at risk such as patients with impaired memory and cognitive functions, patients with visual impairment, patients who have difficulties to follow written instructions, patients who split their weekly oral methotrexate dose, patients with co-morbidities and co-medications.

2. Dosing

Methotrexate should only be prescribed by physicians with expertise in the use of methotrexate and a full understanding of the risks of methotrexate therapy.

- **Dosage for Rheumatoid arthritis**

Adults:
In adults with severe, active, classical or definite rheumatoid arthritis who are unresponsive or intolerant to conventional therapy, Methotrexate should be taken as 7,5 mg orally once a week. The prescriber may specify the day of intake on the prescription.

Elderly:
Methotrexate should be used with extreme caution in elderly patients, a reduction in dosage should be considered.

Children:
Safety and effectiveness in children have not been established, other than in cancer chemotherapy.

- **Dosage for psoriasis**

For the treatment of severe psoriasis 10-25 mg orally, once weekly, is recommended. Dosage should be adjusted according to the patient's response and the haematological toxicity. The prescriber may

specify the day of intake on the prescription.

For the indications of rheumatoid arthritis and psoriasis:

Important warning about the dosage of Methotrexate

In the treatment of rheumatoid arthritis and psoriasis, Methotrexate **must only be taken once a week.** Dosage errors in the use of Methotrexate can result in serious adverse reactions, including death. Please read this section of the summary of product characteristics very carefully.

The prescriber should ensure that patients or their carers will be able to comply with the once weekly regimen.

- **Dosage for cancer treatment**

A test dose of 5-10 mg parenterally is recommended, one week prior to therapy to detect idiosyncratic adverse events. Single doses, not exceeding 30 mg/m^2, on not more than 5 consecutive days. A rest period of at least two weeks is recommended between treatments, in order to allow the bone marrow to return to normal.

Doses in excess of 100 mg are usually given parenterally, when the injectable preparation should be used. Doses in excess of 70 mg/m^2 should not be administered without leucovorin rescue (folinic acid rescue) or assay of serum methotrexate levels 24-48 hours after dosing.

If methotrexate is administered in combination chemotherapy regimens, the dosage should be reduced, taking into consideration any overlapping toxicity of the other drug components.

3. Risks associated with overdose

In EU/EEA, despite the risk minimisation measures in place, cases of medication errors are still occurring. In order to assess the root causes and the impact of the risk of medication errors due to inadvertent daily dosing instead of weekly dosing, the PRAC considered the analyses of cases report of inadvertent daily instead of weekly usage of methotrexate-containing products, including reports without adverse events, for the period 1 January 2013 until 31 March 2018 from the EudraVigilance database as well as from the data provided by the Marketing Authorisation Holders (MAHs) of methotrexate-containing products which included analyses of the medication error case reports from the companies' pharmacovigilance databases and in the literature. **The data showed that severe, life-threatening and fatal cases of overdose due to medication errors with methotrexate-containing medicinal products continue to be reported despite the risk minimisation measures in place.** While daily instead of once weekly use of methotrexate was mainly reported with oral dosage forms in non-oncologic indications, predominantly rheumatoid arthritis and psoriasis, there were also cases with the use of parenteral formulations, as well as many reports which did not specify the route of administration.

4. Informing/Discussing with the patients/caregivers

Healthcare professionals who prescribe or administer methotrexate for inflammatory diseases should:

- provide the patient/caregiver with detailed and clear dosing instructions for once-weekly dosing, without using abbreviations,
- carefully check in every new prescription/administration that the patient/caregiver comprehends that the medicine should be used once weekly,
- decide in common with the patient/caregiver on which day of the week the patient will be administered methotrexate,
- inform the patient/caregiver of overdosing signs and guide the patient/caregiver to seek immediately medical advice in the case of suspected overdosing.

Important REMINDER FOR THE COMMUNITY PHARMACISTS

As the Community Pharmacists are the most accessible health professionals to the public and are becoming increasingly involved in primary health care, they are all reminded to counsel the patient regarding the risk of medication errors due to inadvertent daily instead of once-weekly dosing.

5. Additional Risk Minimization Measures

Further measures will be implemented for the prevention of dosing errors, including clear warnings in the outer and inner packaging as well as updates in the Summary of Product Characteristics and the Patient Information Leaflet. For the oral formulations, besides the distribution of this educational material for healthcare professionals (current document), a patient card will be provided with every packaging.

The development of patient card is considered a necessary tool to remind patients to take the product only once weekly, inform on serious adverse effects that may be fatal, on the symptoms of overdose and steps to be taken should symptoms arise, and recommend patients to show the card and alert any healthcare professionals not familiar with their methotrexate treatment about their once weekly dosing schedule (e.g. on hospital admission, change of care). The day of the week methotrexate treatment should be taken should be written on the card by the patient. In Appendix 1, a sample of the Patient Card can be found.

Furthermore, the tablets will be available only in blisters.

Lastly, Remedica Ltd has created a targeted follow-up questionnaire, for all medication errors reported with methotrexate and resulting in overdose, in order to gain further knowledge on the reasons leading to medication errors and prevent them adequately, as well as in support of the measurement of the effectiveness of the agreed risk minimisation measures.

6. Adverse Reaction(s) reporting

Suspected Adverse Drug Reactions (side effects) or medication errors may be reported using the Medicines Authority ADR reporting form, which is available online at http://www.medicinesauthority.gov.mt/adrportal, and sent by post or email to; P: Pharmacovigilance Section at Post-Licensing Directorate, Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000 E: postlicensing.medicinesauthority@gov.mt .

Remedica Contact Point

Alternatively, the suspected adverse drug reactions can also be reported to Remedica's Drug Safety Department, via email: drugsafety@remedica.com.cy / a.vasiliou@remedica.com.cy or by phone: 00357 25 553 000.

Andreas Vasiliou
Drug Safety Manager / QPPV
Remedica Ltd

Appendix 1 – Patient Card

IMPORTANT – PATIENT CARD

Methotrexate 2.5 mg film-coated tablets

Carry this card with you at all times

THIS PATIENT CARD IS ONLY INTENDED FOR PATIENTS WHO USE A METHOTREXATE-CONTAINING MEDICINE FOR RHEUMATOID ARTHRITIS AND PSORIASIS.

IF YOU USE METHOTREXATE FOR ONE OF THE ABOVE MENTIONED INDICATIONS, YOU SHOULD ONLY TAKE METHOTREXATE ONCE A WEEK

Write here in full the day of the week for intake: _____

Do not take more than the prescribed dose.

Overdose could lead to serious adverse effects and may be fatal. Symptoms of overdose are e.g. sore throat, fever, mouth ulcers, diarrhoea, vomiting, skin rashes, bleeding or unusual weakness. If you think you have taken more than the prescribed dose, consult a physician immediately.

This medicine has been prescribed for you by a physician with expertise in the use of methotrexate.

Always show this card to health care professionals not familiar with your methotrexate treatment to alert them about your once weekly use (e.g. on hospital admission, change of care).

For more information, please read the patient leaflet inserted in the package.