New measures to avoid potentially fatal dosing errors with methotrexate for inflammatory diseases

26.09.2019 | Circular Number P18/2019

Information on Methotrexate-containing products

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

- Treatment of cancer for which the dosing frequency depends on the regimen and can involve daily administration of methotrexate
- Treatment of inflammatory diseases including rheumatoid arthritis, psoriasis and Crohn's disease, which require once-weekly use of a low dose of methotrexate
- Methotrexate can be taken orally or given by injection.

In Malta methotrexate-containing products are authorised through various procedures (Annex I).

Information from the EMA about the potentially fatal dosing errors associated with methotrexate for inflammatory diseases.

The Pharmacovigilance Risk Assessment Committee (PRAC) started a review on methotrexate medicines, under Article 31 of Directive 2001/83/EC, following the request of Spain.

EMA has recommended new measures to prevent serious and potentially fatal errors with the dosing of methotrexate for treating inflammatory diseases such as rheumatoid arthritis, psoriasis and Crohn's disease. The recommendations result from a review of reports that patients are using methotrexate incorrectly despite previous measures to prevent errors:

For inflammatory conditions, methotrexate must be used just once a week. Using methotrexate more frequently than intended can result in serious side effects. The review found that the error in dosing frequency can occur at any step from prescribing the medicine to the patient taking it.

The new measures to prevent errors were agreed after consultation with patients and healthcare professionals and include:

- Restricting who can prescribe these medicines
- Warnings on the packaging more prominent

In addition, educational material for oral formulations will be distributed to healthcare professionals and a patient card will be provided with each package and tablets will only be available in blister packs.

The CHMP opinion will be forwarded to the European Commission, which will issue a final, legally-binding decision applicable in all EU Member States in due course.

In Malta

For Healthcare Professionals

Healthcare professionals should follow these recommendations:

- Methotrexate for inflammatory conditions is intended for use just once a week. Serious side effects including fatalities have occurred when methotrexate is taken more often
- Only physicians with expertise in using methotrexate medicines are recommended to prescribe them
- Healthcare professionals who prescribe or dispense methotrexate for inflammatory conditions should:
  - Read the educational materials for oral methotrexate medicines
  - Ensure that they are familiar with the latest changes to the summaries of product characteristics for methotrexate medicines used for inflammatory conditions
  - Give clear instructions to the patient (or carer) about once-weekly dosing
  - Check carefully that the patient (or carer) understands that the medicine must be used once a week, and do this each time a new prescription is issued or the medicine is dispensed
  - Decide together with the patient (or carer) on which day of the week the patient uses methotrexate
  - Counsel the patient (or carer) about signs of methotrexate overdose and give instructions to promptly seek medical advice in case of suspected overdose.

A DHPC letter about the safety concern will be disseminated to HCPs in Malta. Archived DHPC letters are available online at http://www.medicinesauthority.gov.mt/dhpc

Information for Patients

- If you are taking methotrexate for rheumatoid arthritis, psoriasis or Crohn's disease, you must take it just once a week
- Take your methotrexate medicine on the same day every week
- Follow the instructions on the packaging of your methotrexate medicine
- You will receive a patient card with your methotrexate tablets (or oral liquid). Read it carefully because it tells you how to take your medicine
- Show your patient card to any new healthcare professional who treats you so that they know that you take your methotrexate medicine once a week
- See your doctor at once if you get a sore throat, fever, mouth ulcers, diarrhoea, vomiting, skin rashes, bleeding or unusual weakness. These can be signs of taking too much methotrexate
- Always attend your scheduled clinic visits and blood test appointments. They are important for making sure that your methotrexate medicine is working and that it is not causing any concern

- If you are not sure about how to take your methotrexate medicine or you have any questions about it, talk to your doctor or pharmacist.

For more information please see the European Medicines Agency's Methotrexate-containing medicines referral page.

Reporting Adverse Drug Reactions

Healthcare professionals and patients are encouraged to maintain vigilance on Methotrexate-containing medicines. Suspected Adverse Drug Reactions (side effects) may be reported using the Medicines Authority Form and sending it to Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000 or online to **http://www.medicinesauthority.gov.mt/adrportal** or to the marketing authorisation holder or their local representatives.

Post-Licensing Directorate
Medicines Authority

Healthcare professionals and patients are encouraged to regularly check the Medicines Authority website for product safety updates as these are issued on an ongoing basis.

Annex I

In Malta the following products are authorised through various procedures

Active Ingredients	Product Name	Pharmaceutical Form	Classif-cation	Authorisation Number	MAH/license holder
METHOTREXATE 25 milligram(s)/millilitre	Methotrexate 25mg/ml solution for injection (2ml Vial)	Solution for injection	POM	MA1269/04701	Accord Healthcare Ireland Ltd
METHOTREXATE 100 milligram(s)/millilitre	Methotrexate 100mg/ml Concentrate for solution for infusion (5ml vial)	Concentrate for solution for infusion	POM	MA1269/04704	Accord Healthcare Ireland Ltd
METHOTREXATE 100 milligram(s)/millilitre	Methotrexate 100mg/ml Concentrate for solution for infusion (10ml vial)	Concentrate for solution for infusion	POM	MA1269/04705	Accord Healthcare Ireland Ltd
METHOTREXATE 100 milligram(s)/millilitre	Methotrexate 100mg/ml Concentrate for solution for infusion (50ml vial)	Concentrate for solution for infusion	POM	MA1269/04706	Accord Healthcare Ireland Ltd
METHOTREXATE 25 milligram(s)/millilitre	Methotrexate 25mg/ml solution for injection (20ml Vial)	Solution for injection	POM	MA1269/04702	Accord Healthcare Ireland Ltd
METHOTREXATE 25 milligram(s)/millilitre	Methotrexate 25mg/ml solution for injection (40ml Vial)	Solution for injection	POM	MA1269/04703	Accord Healthcare Ireland Ltd
METHOTREXATE 2.5 milligram(s)	Methotrexate 2.5mg Tablets	Tablets	POM	MA1269/06901	Accord Healthcare Ireland Ltd
METHOTREXATE 10 milligram(s)	Methotrexate 10mg Tablets	Tablets	POM	MA1269/06902	Accord Healthcare Ireland Ltd
METHOTREXATE 2.5 milligram(s)/millilitre	Methotrexate 2.5mg/ml Solution for Injection	Solution for Injection	POM	AA734/00201	Hospira UK Limited
METHOTREXATE 25 milligram(s)/millilitre	Methotrexate 25mg/ml Solution for Injection	Solution for Injection	POM	AA734/00202	Hospira UK Limited
METHOTREXATE 100 milligram(s)/millilitre	Methotrexate Solution for Injection 100mg/ml	Solution for Injection	POM	AA734/00203	Hospira UK Limited
METHOTREXATE 2.5 milligram(s)	Methotrexate Tablets 2.5mg	Tablets	POM	AA996/00401	Morningside Healthcare Limited

Active Ingredients	Product Name	Pharmaceutical Form	Classif-cation	Authorisation Number	MAH/license holder
METHOTREXATE 100 milligram(s)/millilitre	Methotrexate Solution for Injection 1g/10ml	Solution for Injection	POM	AA505/09501	Pfizer Hellas S.A.
METHOTREXATE 25 milligram(s)/millilitre	Methotrexate Solution for Injection 50mg/2ml	Solution for Injection	POM	AA505/09502	Pfizer Hellas S.A.
METHOTREXATE 2.5 milligram(s)/millilitre	Methotrexate Solution for Injection 5mg/2ml	Solution for Injection	POM	AA505/09503	Pfizer Hellas S.A.
METHOTREXATE 100 milligram(s)/millilitre	Methotrexate Solution for Injection 5g/50ml	Solution for Injection	POM	AA505/09504	Pfizer Hellas S.A.
METHOTREXATE 25 milligram(s)/millilitre	Methotrexate Solution for Injection 500mg/20ml	Solution for Injection	POM	AA505/09505	Pfizer Hellas S.A.
METHOTREXATE 2.5 milligram(s)	Methotrexate 2.5mg film-coated tablets	Tablets	POM	AA084/05701	Remedica Limited
METHOTREXATE	Jylamvo	Oral solution	POM	EMEA/H/C/003756	Therakind (Europe) Limited
METHOTREXATE	Nordimet	Solution for injection	POM	EMEA/H/C/003983	Nordic Group B.V..

Feedback Form

The Medicines Authority thanks you for the time taken to read this safety circular. The dissemination of safety circulars is an important process whereby Regulatory Authorities can communicate important issues with respect to the safety of medicines, in order to protect and enhance public health

The Medicines Authority kindly invites your anonymous feedback about the regulatory action being communicated. This may be returned by folding this formt (address side up), stapling the ends and then posting (no stamp required)

Feedback:

We thank you for your interest and look forward to hearing your opinion.

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Pharmacovigilance Section

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Medicines Authority

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