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Direct Healthcare Professional Communication (DHPC)

Recommendations to avoid potentially fatal dosing errors when using methotrexate for inflammatory diseases

Dear Healthcare Professional,

Accord Healthcare Ireland Limited, Hospira UK Limited, Morningside Healthcare Limited, Pfizer Hellas S.A, Remedica Ltd, Therakind (Europe) Limited in agreement with the European Medicines Agency and the Malta Medicines Authority would like to inform you of the following:

Summary

- **Dosing errors with serious consequences, including fatalities, have been reported when methotrexate intended for once-weekly use in inflammatory diseases was taken daily**
- **Only physicians with expertise in using methotrexate-containing medicines should prescribe them**
- **Healthcare professionals who prescribe or dispense methotrexate for inflammatory diseases should:**
    - **Provide to the patient/carer complete and clear dosing instructions on the once-weekly dosing**
    - **Check carefully at every new prescription /dispensing that the patient/carer understands that the medicine must be used once weekly**
    - **Decide together with the patient/carer on which day of the week the patient uses methotrexate**
    - **Inform the patient/carer of signs of overdose and instruct them to promptly seek medical advice in case of suspected overdose.**

Background on the safety concern

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

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

Despite measures already taken to prevent dosing errors, serious, sometimes fatal, cases continue to be reported, in which patients being treated for inflammatory diseases have taken methotrexate daily instead of once weekly. A safety review performed at EU level found that these errors can occur at all stages of the medication process.

Therefore, further measures to prevent dosing errors will be introduced, including prominent warnings on outer and inner packaging and updates to the summary of product characteristics and package leaflet. For **oral formulations**, there will be educational materials for healthcare professionals and a patient card will be provided with each package. In addition, tablets will only be available in blister packs.

Call for reporting

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are reminded to continue to report suspected adverse reactions associated with methotrexate-containing products in accordance with the national spontaneous reporting system. Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to Post-licensing directorate, Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000, Malta or sent by email to postlicensing.medicinesauthority@gov.mt.

Company contacts

Should you have any question or require additional information, please call Medical Information at:

Company	Product Name	Email	Phone
Accord Healthcare Ireland Limited	Methotrexate 25mg/ml solution for injection (2ml Vial)	kunal_more@accord-healthcare.com regulatoryAffairsIreland@accord-healthcare.com jackie_roberts@accord-healthcare.com	+44 02088631427
	Methotrexate 25mg/ml solution for injection (20ml Vial)		
	Methotrexate 25mg/ml solution for injection (40ml Vial)		
	Methotrexate 100mg/ml Concentrate for solution for infusion (5ml vial)		
	Methotrexate 100mg/ml Concentrate for solution for infusion (10ml vial)		
	Methotrexate 100mg/ml Concentrate for solution for infusion (50ml vial)		
	Methotrexate 2.5mg Tablets		
	Methotrexate 10mg Tablets		

Company	Product Name	Email	Phone
Hospira UK Limited	Methotrexate 100 mg/ml Injection	Safety@drugsalesltd.com	+356 21419070/1/2
	Methotrexate 2.5mg/ml Solution for Injection		
	Methotrexate 25mg/ml Solution for Injection		
Morningside Healthcare Ltd	Methotrexate 2.5mg Tablet	jhibbert@morningsidehealthcare.com	+44 1162045950
	Methotrexate 10mg Tablet		
Pfizer Hellas S.A.	Methotrexate 1 g/10 ml Injection	Safety@drugsalesltd.com	+356 21419070/1/2
	Methotrexate 5 mg/2 ml Injection		
	Methotrexate 500mg/20mL Injection		
	Methotrexate 50mg/2 ml Injection		
	Methotrexate 5g/50mL Injection		
Remedica Ltd	Methotrexate 2,5 mg film-coated tablets	a.vasiliou@remedica.com.cy drugsafety@remedica.com.cy	+357 25553251
Therakind (Europe) Limited	Jylamvo	jackie.winslade@therakind.com	+44 2083466035

Yours faithfully,

Post-Licensing Directorate

Medicines Authority

Disclaimer

This Direct Healthcare Professional Communication has been submitted to you on behalf of Accord Healthcare Ireland Limited, Hospira UK Limited, Morningside Healthcare Ltd, Pfizer Hellas S.A, Remedica Ltd, Therakind (Europe) Limited

Annexes

The following measures shall be implemented by Marketing Authorisation Holders:

All methotrexate-containing products	Each MAH should implement the agreed targeted follow-up questionnaires for all medication errors resulting in overdose
Methotrexate-containing products for oral use with at least one indication requiring once weekly dosing	Each MAH should operate a risk management system to be described in a risk management plan (RMP) which shall be submitted to the relevant Competent Authorities. The RMP should reflect the following additional risk minimisation measures to address the important identified risk of medication errors resulting in overdose: - educational material(s) for healthcare professionals developed in accordance with the key elements agreed; - the agreed patient card
For tablet formulations	MAHs should replace any bottle or tube used as immediate packaging by blisters.