Medical Safety Information
Pharmaceuticals and Medical Devices Agency
No. 6 October, 2008

Precautions against misuse (overdose) of antirheumatic methotrexate preparations

POINT Key points for safe use

(Case 1) A patient was treated with methotrexate for rheumatoid arthritis in a hospital, but transferred to another hospital with a different disease. Since the patient accidentally administered without rest period methotrexate he brought in, the patient experienced myelosuppression.

1 How to take antirheumatic methotrexate preparations

- **Methotrexate for treatment of rheumatoid arthritis should be used on a special dosing regimen requiring rest period (no drug time).**

〈An example of dosing schedule〉 The following treatment cycle should be repeated on a weekly basis.

Day 1		Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Morning dose	Evening dose	Morning dose	Rest period (no drug time)				

Please refer to the section of “dosage and administration” in the package inserts. Additional indication, dosage, and administration for juvenile “idiopathic arthritis with joint symptoms” was approved in September 2008. Caution should be exercised when using the drug.

Serious adverse reactions may occur when methotrexate is accidentally administered without rest period!

Please remember that use of methotrexate for treatment of rheumatoid arthritis requires rest period (no drug time)!

(Case 2) A patient with rheumatoid arthritis brought a methotrexate preparation with no date and time of dosing indicated in the space provided. The patient was treated with methotrexate without rest period and experienced leucopenia.

2 Precautions for handling antirheumatic methotrexate preparations – 1

- Date and time of dosing should be indicated in the space provided on the package sheet when the drug is dispensed.
- When the drug is dispensed, the package sheet should not be cut off and the patient should be instructed not to cut it off.

Precautions according to the form of packaging containers – 1

Rheumatrex Capsules 2mg
(Wyeth K.K.)

Methotrexate Cap. 2mg "Mylan"
(Mylan Seiyaku Ltd.)

Trexamette
(Shiono Chemical Co., Ltd.)

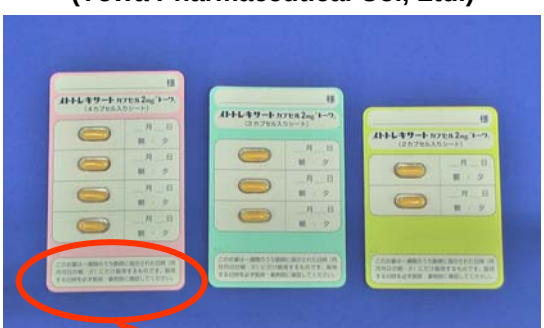
METHOTREXATE Cap. 2mg "SAWAI"
(Sawai Pharmaceutical Co., Ltd.)

Dosing date

Month/Date
(Day of the week)

Morning/Evening

METHOTREXATE CAPSULES 2mg "TOWA"
(Towa Pharmaceutical Co., Ltd.)



You should take this drug only at the time and date in a week indicated by your physician (Month-Date Morning/Evening). Please make sure to ask your physician/pharmacist about the date and time to take the drug.

Notes about the date and time of dosing are printed on the package of products.

If the package sheets are separated, these notes can be cut off, resulting in accidents.

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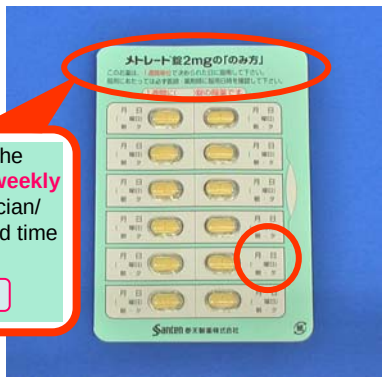
Precautions according to the form of packaging containers – 2

Some products consist of a blister pack set in a separable package sheet. Such products should be dispensed with the blister pack set in position and the patient should be instructed not to separate them.

Dispensing only the separated blister pack may lead to accidents because it does not contain notes on how to take the drug or the date and time of dosing.

The blister packs set in the package sheets

Metolate tablets 2mg
(Santen Pharmaceutical Co., Ltd.)



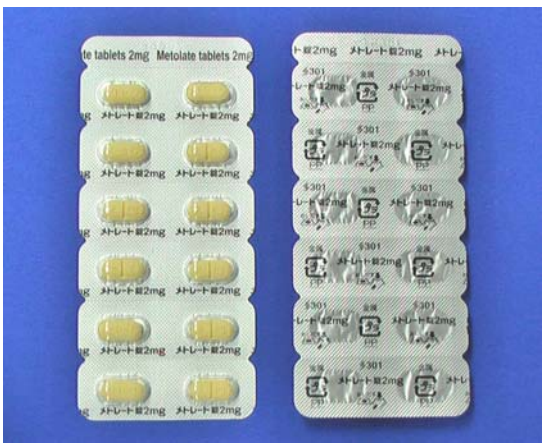
You should take this drug at the indicated date and time in **a weekly cycle**. Please ask your physician/ pharmacist about the date and time to take the drug.

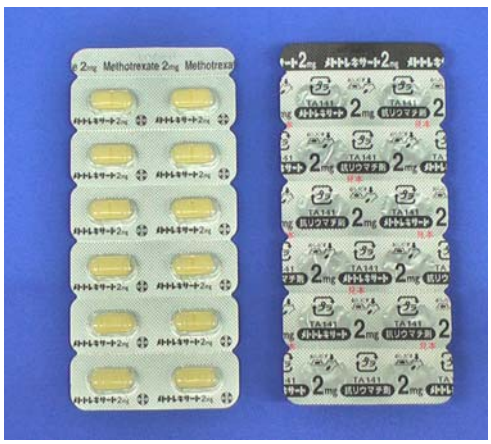
( ) tablet(s) per week

Methotrexate 2mg
(Mitsubishi Tanabe Pharma Corporation)

Month/Date
(Day of the week)
Morning/Evening

Separated blister packs





(Case 3) Insufficient contents of the referral form for a patient referred to a different hospital resulted in an improper dosage regimen of the methotrexate preparation.

3 Precautions for handling antirheumatic methotrexate preparations – 2

- The drugs brought by a patient on admission to a hospital should be checked carefully using a Medical Diary or the referral form. Any questions should be addressed to the prescribing physician.
- Prescriptions and referral forms should indicate the time, date, and number of dosing clearly in detail.

When a patient brings the drugs, the dosing regimen should be checked using a Medical Diary and other materials.

Prescriptions and referral forms should clearly indicate the time, day of the week, and the number of tablets for dosing.

The Ministry of Health, Labour and Welfare (MHLW) issued notifications related to PMDA Medical Safety Information No. 6:

●"Preventive measures against medical accidents regarding misuse (overdose) of antirheumatic methotrexate preparations" (PFSB/SD Notification No. 0829001) issued by the Safety Division of the Pharmaceutical and Food Safety Bureau, MHLW, on August 29, 2008. Based on this notification, the manufacturers of antirheumatic methotrexate preparations are now working to change the package designs.

●"Handling of the antirheumatic methotrexate preparations for prevention of misuse (overdose) (precautions)" Joint Notification of HPB/GAD, No. 1020001 issued by the General Affairs Division of the Health Policy Bureau, PFSB/GAD No. 1020001 issued by the General Affairs Division of the Pharmaceutical and Food Safety Bureau, and PFSB/SD No. 1020001 issued by the Safety Division of the Pharmaceutical and Food Safety Bureau, MHLW.

Information on these notifications are available at the Pharmaceuticals and Medical Devices Information website (in Japanese)
http://www.info.pmda.go.jp/iryoujiko/file/20080829.pdf
http://www.info.pmda.go.jp/iryoujiko/file/20081020.pdf

Information on the package inserts of the antirheumatic methotrexate preparations listed in this Medical Safety Information is also available at the Pharmaceuticals and Medical Devices Information website (in Japanese)
http://www.info.pmda.go.jp/psearch/html/menu_tenpu_base.html

About this information

* PMDA Medical Safety Information is issued by the Pharmaceuticals and Medical Devices Agency for the purpose of providing healthcare providers with clearer information from the perspective of promoting the safe use of pharmaceuticals and medical devices. The information presented here has been compiled, with the assistance of expert advice, from cases collected as Medical Accident Information Reports by the Japan Council for Quality Health Care, and collected as Adverse Drug Reaction and Malfunction Reports in accordance with the Pharmaceutical Affairs Law.
* We have endeavored to ensure the accuracy of this information at the time of its compilation but do not guarantee its accuracy into the future.
* This information is not intended to impose constraints on the discretion of healthcare professionals or to impose obligations and responsibility on them, but is provided as a support to promote the safe use of pharmaceuticals and medical devices by healthcare professionals.

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