12 April 2018
EMA/227227/2018

PHARMACOVIGILANCE RISK ASSESSMENT COMMITTEE (PRAC)

List of questions to be addressed by healthcare professional representative organisations

Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data
Procedure No: EMEA/H/A-31/1463

Active substances	Methotrexate
Background:	The European Medicines Agency (EMA) has started a review looking at medication errors with methotrexate containing medicinal products. More specifically, the Pharmacovigilance and Risk Assessment Committee (PRAC), the Agency's expert body on medicines safety, is looking into medication errors due to daily instead of weekly administration, and will evaluate the effectiveness of risk minimisation measures intended to prevent such errors. In the context of this review, the PRAC considers that it would be useful to obtain additional information from healthcare professional organisations on the points covered by the set of questions below. For further details on this review please see here
Timelines	Responses requested by **31 May 2018**

Name of organisation consulted: **Prescrire**

Prescrire is a non-profit continuing education organisation that works to improve the quality of patient care. *Prescrire* publishes reliable information about treatments and treatment strategies, in total independence, as a basis for truly informed decision-making. *Prescrire* is funded exclusively by its subscribers. It receives no other financial support whatsoever and carries no advertising. It has no shareholders or sponsors. *Prescrire* is an active member of the **International Medication Safety Network** (IMSN), which aims to prevent medication errors and contribute to safer healthcare.
For many years *Prescrire* has raised subscribers' awareness on preventable methotrexate overdoses (1-16).

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

More info: english.prescrire.org; contact@prescrire.org

Question 1

Are you aware of any data that would help us assess the root-causes for medication errors due to daily instead of weekly administration?

If yes, please provide such data.

Response from **Prescrire**:

Methotrexate overdoses may result from daily instead of weekly administration, a particular type of medication error relating to a wrong frequency of administration, but result also from various types of medication errors at various stages of the medicine use process (prescribing, dispensing, administration or self-care). Therefore attention should be paid to the fact that addressing only the specific part of periodicity errors is misleading for assessing the root-causes for erroneous methotrexate overdoses.

A very weak surveillance of medication errors associated with methotrexate

Serious adverse events related to methotrexate overdose due to erroneous daily intake of the intended weekly dose, including fatalities, are still occurring, although they have been known for a long time. In fact, the surveillance of this problem appears very weak, with few studies following the seminal Institute for Safe Medication Practices (IMSP) study on the FDA Adverse Event Reporting System (AERS) between November 1997 and December 2001 (17). Further in the US, analysts examined all medication error reports submitted to the Pennsylvania Patient Safety Authority from June 2004 through July 2010 mentioning methotrexate (18).

In Denmark, four databases were searched between 1999 and 2011: the Danish Patient Safety Databases (DPSD), controlled by the Danish National Agency for Patients' Rights and Complaints, the Patient Compensation Association (PCA), the Danish Poison and Information Centre (DPIC), and the online database of the Department for Patient Complaints (DPC) (19).

In Australia, three report databases were reviewed: the National Coronial Information System (NCIS, 2000-2014), the Therapeutic Goods Administration Database of Adverse Event Notifications (TGA DAEN, 2004-2014) and Australian Poisons Information Centres (PICs, 2004-2015) (20).

At European level, the few data on erroneous daily dosing of methotrexate are only available in the Spanish referral notification. The search into EudraVigilance using the public web service www.adrreports.eu do not provides reliable results. Therefore, the assessment undertaken by the PRAC should include an epidemiological approach in order to complete the Spanish referral notification.

Roots causes not to be overlooked: regulation, packaging, labelling and awareness

Although methotrexate started to be used in psoriasis and rheumatoid arthritis as early as the 1970s, marketing authorizations were granted from the 1990s in these indications; a regulatory fact to be considered as a root cause of the occurrence of these errors, which are fatal because of the known nature of the cytotoxic substance. It is regrettable today that a preliminary risk analysis (also called FMEA: failure mode and effect analysis) was not carried out by the granting authorities when this cytotoxic was authorized in non-oncologic indications.

A previous action from the CHMP Pharmacovigilance Working Party (PhVWP) on December 2011 emphasised two main proposals: 1) on product information for methotrexate for oral use in rheumatologic and dermatologic indications (statement "take the prescribed dose once a week" for printing on the package (labelling), preferably on the vial's cap); 2) on patient information on the risk

of overdose due to erroneous daily intake of the intended weekly dose (21).

Even prominent, the warning statement printed on the box and the patient leaflet is overlooked by patients and healthcare professionals (10). Such failures show that this warning is not sufficient to ensure the safety. Therefore professionals should specify the day of the week scheduled for administration on the outer package as a precautionary measure.

The bulk packaging of methotrexate should not have been authorized because it exposes to the risk of massive accidental ingestions and prevent the doses actually taken to be counted. The false good idea that a cap would make handling of bulk bottles by patients with rheumatoid arthritis easier overlooked the fact it made it easier to open by a child (5,9). To what extent have the drug agencies already considered a new type of packaging with the dual objective of preventing child access to the drug while facilitating handling by adults with gripping difficulties (9,14)?

Methotrexate overdoses may be also caused by confusions between different strengths: in addition to the 2.5 mg tablets, the 10 mg tablets expose to a fourfold risk of error at all stages of the process (prescribing, dispensing, administration or self-care), which is also increased by similar packaging (6). *Prescrire* found that the 2.5 mg methotrexate tablet in the Imeth° range should lead to the withdrawal of the 10mg tablet, which exposes to confusions, without providing any benefit (11).

In particular circumstances, such as transitions of care (i.e. medicines brought by a patient when hospitalised), root causes related to packaging, labelling and awareness play an important role in facilitating methotrexate dosing errors (10).

Question 2

Please provide any data and/or information on the implementation of risk minimisation activities aimed at preventing medication errors with methotrexate containing medicinal products.

The information we would like to receive could include clinical guidelines and protocols, results of surveys among members of your organisations, questionnaires circulated, literature publications, any other method / initiative to measure whether these activities had a significant impact on the behaviour of healthcare professionals, the patients and any changes observed in clinical practice related to these products etc. or any other information that you would like to share.

Response from **Prescrire**:

Most recommendations available come from IMSN members

The assessment of the CHMP Pharmacovigilance Working Party (PhVWP) on December 2011 referred only to publications from members of the International Medication Safety Network (IMSN) (21-24). In fact, Prescrire and the Institute for Safe Medication Practices Canada developed cornerstone recommendations based on previous work by the Institute for Safe Medication Practices (ISMP) and the NHS National Patient Safety Agency (25-28).

Further recommendations have been published elsewhere involving numerous IMSN members (29-36).

Regular monitoring of methotrexate overdoses is essential to measure progress in improving their prevention

In the UK, where such a monitoring is provided by the National Learning and Reporting system (NRLS), it was thought that the measures taken since 2006 had solved the problems because there were no incident reports of death or severe harm in 2007 involving methotrexate (37). After adding the inappropriate administration of daily oral methotrexate to the Never event List in 2011, data summaries from 2012 to 2017 showed that several events still occured each year (38).

This suggests that the prevention of practice-related errors still need to be strengthened, with stronger safety barriers incorporated into the packaging and labelling to involve the end-user.

Still room for improving methotrexate packaging and patient information

Since our 2007 review, *Prescrire*'s proposals for preventing oral methotrexate overdose has added to the principles that healthcare professionals, patients and non-professional carers must observe (prescribing plan; patient treatment history; involving patients in their own safety) that the packaging should be designed to facilitate these safety measures. Regulators and manufacturers should ensure that methotrexate tablets are packaged in unit-dose blister packs equipped with a safety film, and adapted to patients' clinical condition. The packaging should also include a leaflet clearly specifying the weekly dose regimen and a treatment follow-up diary (3).

In 2013, *Prescrire* renewed these proposals, including the need for appropriate packaging for once-weekly dosing (10). These proposals were consistent with the IMSN Position Statement (39). Due to the additional risk of confusion between the 2.5 mg and 10 mg dosages, *Prescrire* asked for the withdrawal of 10 mg methotrexate tablets from the market (11).

In January 2018, we agreed with Novatrex° tablets that have been packaged in blister packs since September 2017 in France, and no longer in bulk bottles without child-proof caps. The dangers of methotrexate and the serious consequences of errors in the dosing interval should have warranted a more substantial improvement in the packaging of Novatrex°: for example, a more resistant film covering the blister packs to prevent any possibility of extraction by a child (even if it means providing a tablet-extracting tool for patients whose hands are affected by rheumatoid arthritis); and pre-perforated blister packs which allow each tablet to be identified, and highlight the drug's weekly administration (16).

A few medicines agencies also seek to redesign product packaging to improve safe administration of methotrexate tablets (40).

Prescrire is not the only organization asking to ban bulk bottles of loose tablets or capsules without child-proof caps (in countries where patients packs or compliance packs are not feasible, pharmacist should prepare specific aids with a clear dosing calendar): IMSN, ISMP and New-Zealand support also this position (35,39,41,42).

Raising awareness about fatal methotrexate dosing errors

Healthcare professionals must take time to inform patients, family members and caregivers about the risk; such warnings must be repeated until the severity of methotrexate dosing errors is fully grasped. IMSN members were the first group to design specific patient information, widely before medicines agencies (8,43,44). Some Medicine Agencies have followed this way and provide such materials, i.e. the French Health Products Agency (ANSM) since 2016 (45).

It is the mission of EU drug agencies to better guide and encourage companies to develop packaging that is both safe and patient-friendly, while preserving relatives from accidental ingestion.

29 May 2018,

Review produced collectively by the *Prescrire* Editorial Staff:

no conflicts of interest

References:

1- Prescrire Rédaction "Intoxication aiguë par le méthotrexate" *Rev Prescrire* 1997 ; **17** (177) : 669.
2- Prescrire Rédaction "Méthotrexate : gare au surdosage" *Rev Prescrire* 2002 ; **22** (232) : 665.
3- Prescrire Rédaction "Méthotrexate par voie orale: prévenir les surdoses par erreur" *Rev Prescrire* 2007 ; **27** (283) : 352-355. Tranlated in Prescrire Editorial Staff "Oral methotrexate: preventing avoidable overdose" *Prescrire Int* 2007 ; **16** (90) : 150-152.
4- Prescrire Rédaction "Les propositions Prescrire : Choisir un traitement antirhumatismal dans la polyarthrite rhumatoïde" *Rev Prescrire* 2009 ; **29** (312) : 768.
5- Prescrire Rédaction "Méthotrexate oral : flacons-vrac dangereux pour un cytotoxique" *Rev Prescrire* 2011 ; **31** (331) : 346-347.
6- Prescrire Rédaction "Méthotrexate oral à 10 mg : attention aux surdoses avec ce dosage fort, et un conditionnement à risques" *Rev Prescrire* 2011 ; **31** (331) : 346.
7- Prescrire Rédaction "Méthotrexate hebdomadaire : encore des décès en 2011 en France" *Rev Prescrire* 2011 ; **31** (336) : 747. Translated in: Prescrire Editorial Staff "Weekly methotrexate: still more deaths in France in 2011" *Prescrire Int* 2011 ; **21** (123) : 15.
8- Prescrire Rédaction "Méthotrexate oral une fois par semaine : attention UNE SEULE FOIS !" *Rev Prescrire* 2011 ; **31** (338) : 936.
9- Prescrire Rédaction "Prescrire en questions. Novatrex° : le flacon-vrac de méthotrexate est trop dangereux pour les enfants" *Rev Prescrire* 2012 ; **32** (340) : 156.
10- Prescrire Rédaction "Méthotrexate oral hebdomadaire : informer du risque d'erreur mortelle" *Rev Prescrire* 2013 ; **33** (352) : 101. Translated in: Prescrire Editorial Staff "Weekly oral methotrexate therapy: raise awareness of fatal dosing errors" *Prescrire Int* 2013 ; **22** (138) : 126.
11- Prescrire Rédaction "Imeth° 2,5 mg de méthotrexate : gare aux confusions avec Imeth° 10 mg" *Rev Prescrire* 2013 ; **33** (355) : 346.
12- Prescrire Rédaction "Gamberges - remue-méninges : Faute ou erreur ?" *Rev Prescrire* 2013 ; **33** (360) : 724.
13- Prescrire Rédaction "Prescrire en questions. Cartons rouges et jaunes du Palmarès 20103 du conditionnement (suite)" *Rev Prescrire* 2014 ; **34** (365) : 265-1-265-3.
14- Prescrire Rédaction "Technosécurisation" *Rev Prescrire* 2016 ; **36** (398) : 884.
15- Prescrire Rédaction "Méthotrexate hebdomadaire en stylos préremplis - Metoject°, Nordimet°. Des injections plus simples, mais vérifier le dosage avec soin" *Rev Prescrire* 2017 ; **37** (404) : 405-406.
16- Prescrire Rédaction "Méthotrexate oral hebdomadaire - Novatrex° : en plaquettes" *Rev Prescrire* 2018 ; **38** (411) : 18. Translated in: Prescrire Editorial Staff "Oral weekly methotrexate (Novatrex°): in blister packs" *Prescrire Int* 2018; **27** (192): 95.
17- Moore TJ et coll. "Reported medication errors associated with methotrexate" *Am J Health Syst Pharm* 2004; **61** (13): 1380-1384.
18- Pennsylvania Patient Safety Authority "Data Snapshot: Errors Involving Methotrexate" *Pa Patient Saf Advis* 2011; 8 (2): 77-79.
19- Perregaard H et coll. "Medication errors detected in non-traditional databases: types of errors in methotrexate dosing as listed in four different Danish registers" *Eur J Clin Pharmacol* 2015; **71** (11): 1375-1379.
20- Cairns R et coll. "A decade of Australian methotrexate dosing errors" *Med J Aust* 2016; **204** (10): 384.e1-384.e6.
21- EMA "CHMP Pharmacovigilance Working Party (PhVWP) December 2011 plenary meeting. Monthly report: issue 1112" 10 January 2012; 5 pages.
http://www.ema.europa.eu/docs/en_GB/document_library/Report/2012/01/WC500120115.pdf
22- Prescrire Editorial Staff "Oral methotrexate: preventing avoidable overdose" *Prescrire Int* 2007; **16** (90): 150-152.
23- Blinova E, Volling J, Koczmara C, Greenall J. "Oral methotrexate: preventing inadvertent daily administration" *Can J Hosp Pharm.* 2008; **61** (4): 275-277.

24- Institute for Safe Medication Practices Canada "Incidents of inadvertent daily administration of methotrexate" *ISMP Can Saf Bull* 2008; 8(2):1-2.
25- Institute for Safe Medication Practices (ISMP) "Beware of erroneous daily oral methotrexate dosing" *ISMP Medication Safety Alert!* 2002; **7** (7): 1-2.
26- NHS National Patient Safety Agency "Towards the safer use of oral methotrexate" 2004; 30 pages.
27- NHS National Patient Safety Agency "Patient safety alert 03 - Reducing the harm caused by oral methotrexate" 29 July 2004; 4 pages.
28- NHS National Patient Safety Agency "Patient safety alert 13 - Improving compliance with oral methotrexate guidelines" 1 June 2006; 8 pages.
29- Irish Medication Safety Network "IMSN Safety Alert: Oral Methotrexate Safety Alert" May 2010; 1 page.
30- Health Quality & Safety Commission New Zealand "Medication Alert 14 - Oral Methotrexate - once weekly dosing" April 2012; 2 pages.
31- Sécurité des patients Suisse "Quick-Alert No 28 Intoxication au méthotrexate -> Éviter les surdosages par voie orale" 5 Décembre 2012 ; 4 pages.
32- Institute for Safe Medication Practices Canada Canada "Severe harm and deaths associated with incidents involving low-dose methotrexate" *ISMP Canada Safety Bulletin.* 2015; 15 (9):1-5.
33- Institute for Safe Medication Practices (ISMP) "Severe harm and death associated with errors and drug interactions involving low-dose methotrexate" *ISMP Medication Safety Alert!* 2015; **20** (20): 1-5.
34- Institute for Safe Medication Practices (ISMP) "Another mistaken methotrexate prescription" *PharmacyToday* March 2016: 88.
35- Health Quality & Safety Commission New Zealand "Reducing the risk of error and patient harm with low-dose oral methotrexate" *Medication Safety Watch* April 2016; (17): 1-2.
36- Styrelsen for Patientsikkerhed "Vær opmærksom på overdosering med methotrexat på grund af daglig behandling i stedet for ugentlig" 7 September 2017.
37- NHS National Patient Agency "Safety in Doses - Improving the use of medicines in the NHS. Learning from national reporting 2007" August 2009; 70 pages.
38- NHS Improvement "Never Events data" https://improvement.nhs.uk/resources/never-events-data/
39- International Medication Safety Network "IMSN Position Paper on Making Medicines Naming, Labelling and Packaging Safer" October 2013; ? pages.
40- Therapeutic Goods Administration (TGA) Australia "Advisory Committee on Medicines - Meeting Statement - Meeting 1, Thursday 2 and Friday 3 February 2017" 18 July 2017; 3 pages.
41- Prescrire Rédaction "Non aux flacons-vrac !" *Rev Prescrire* 2018 ; **38** (411) : 4. Translated in: Prescrire Editorial Staff "No to bulk bottles of loose tablets or capsules!" *Prescrire Int* 2018; **27** (192): 187.
42- Institute for Safe Medication Practices (ISMP) "Simple packaging change could help reduce drug diversion" *ISMP Medication Safety Alert!* 2016; **21** (7): 4.
43- Institute for Safe Medication Practices (ISMP) "Read this important information before taking: Methotrexate" 2012; 2 pages.
44- Institute for Safe Medication Practices Canada "Caution: Not All Medicines Are Taken Every Day" *SafeMedicationUse.ca Newsletter* March 31, 2015; 6 (4).
45- Agence nationale de sécurité du médicament et des produits de santé (ANSM) "Méthotrexate par voie orale = une seule prise par semaine : attention aux erreurs - Point d'information" 14 novembre 2016. http://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Methotrexate-par-voie-orale-une-seule-prise-par-semaine-attention-aux-erreurs-Point-d-information