12 April 2018
EMA/PRAC/199743/2018

PRAC List of questions

To be addressed by the marketing authorisation holder(s) for methotrexate containing medicinal products

Referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Procedure number: EMEA/H/A-31/1463

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1. Background

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

- For the treatment of cancer, such as choriocarcinoma or hematologic cancer, requiring various frequencies of usage including daily usage
- For the treatment of autoimmune diseases, which require immunosuppressive therapy like rheumatoid arthritis, psoriasis, Morbus Crohn and other autoimmune diseases as applicable, requiring weekly usage

Throughout all the years that both indications have been authorized, serious cases, sometimes fatal, by inadvertently taking the product daily instead of weekly for indications that require weekly dosing have been reported.

Several risk minimisation measures were taken in the past by several Member States, but medication errors due to daily usage for non-oncological indications, leading to overdose with serious consequences are still being reported.

Within the last periodic safety update report assessed (covering data from 1st July 2014-30th June 2017) a number of adverse events related to overdose have been reported, in some cases with a fatal outcome.

Furthermore, scientific publications report a significant number of adverse events associated with daily rather than weekly administration of oral methotrexate in non-oncological indications.

On 23 March, Spain notified PRAC about a referral under Article 31 of Directive 2001/83/EC for methotrexate oral formulations, due to serious cases, some of them fatal that have been reported following inadvertently taking the product daily instead of weekly.

The PRAC further agreed during its March 2018 plenary meeting to extend the scope to include also parenteral formulations of methotrexate, as for a high number of cases reported as “incorrect schedule of dose administration” the pharmaceutical form has not been reported, and a low number of cases have also been reported for parenteral formulations.

In addition, the PRAC considered it necessary to perform a EudraVigilance analysis of reports of inadvertent daily instead of weekly usage of methotrexate-containing products. The data to perform this analysis will be provided by EMA and will be evaluated by PRAC together with the responses to the list of questions provided by the MAHs. This EudraVigilance analysis will be provided to all MAHs together with the preliminary assessment reports. PRAC will also liaise with relevant stakeholders as part of the procedure.

2. Questions

The marketing authorisation holders (MAHs) are requested to address the following questions.

Question 1

Please provide

a. an overview of the estimated patient exposure for methotrexate for your marketed products in indications with once weekly treatment courses (e.g. rheumatoid arthritis, psoriasis, Morbus Crohn and other autoimmune indications, if applicable) in each EEA country, the total exposure in the EEA and worldwide exposure for the period 01.01.2013 - 31.03.2018. Please calculate patient exposure by estimating the number of patients exposed based on the usual and most appropriate weekly dose and treatment duration. Patient exposure should be expressed in number of patients and patient-treatment-years. Please differentiate between oral and parenteral formulation.

   Please clearly indicate your method of calculation specifying the assumptions made for weekly dose and duration of treatment and whether the calculated patient exposure relates only to methotrexate of your company or to methotrexate of all MAHs.

Please use the following table:

Table 1: Patient exposure in the EEA and worldwide.

Product name	**Pharmaceutical forms, presentation and strengths**	**Indications**	**EEA country**	**Estimated patient exposure (number of patients)**	**Estimated patient exposure (patient treatment years)**
			EEA:		
			Worldwide:		

Question 2

Each MAH should search its own database for *case reports* of inadvertent daily instead of weekly usage of methotrexate-containing products, including *reports without adverse events* for the period 01.01.2013 - 31.03.2018. The search should not be limited only to reaction field (e.g. appropriate SMQ or HLGT); instead, each MAH should according to its technical possibilities search in additional fields such as case narratives, other free text fields, flags, structured dosing information, etc. Whenever possible, EudraVigilance case numbers for case reports should be provided and used throughout the response document.

Based on the above the MAHs are requested to provide the following:

a. Please provide the total number of serious cases, fatal cases, cases with an outcome of resolved with sequelae or not resolved, non-serious cases and cases without adverse events (e.g. incident, near-incident, potential errors, errors without harm, intercepted errors) in the EEA and worldwide regarding inadvertent daily instead of weekly usage. Data should also be differentiated by oral and parenteral dosage forms.

b. Please provide the number of reported cases stratified per products authorised for non-oncologic and oncologic indications and per products authorized only for non-oncological indications. Please discuss potential differences in observed numbers. Please differentiate between oral and parenteral formulation.

c. Please provide the number of cases of inadvertent daily instead of weekly usage per age group (children up to 12 years, adolescents up to 18 years, adults 18-64 years, patients 65-75 years, elderly over 75 years) for the whole EEA as well as stratified by country and by formulation.

d. Please perform a detailed root cause analysis for cases of inadvertent daily instead of weekly usage in the period 01.01.2013 - 31.03.2018 in the EEA. Please provide details on the stage of medication process where the error occurred. Reference is made to available guidance in this field. Please discuss whether different root causes could be related to specific characteristics of the healthcare system or patient care. Please also provide information on how and who has identified the medication error. Any additional relevant information on root cause of inadvertent daily instead of weekly methotrexate usage should be provided and discussed.

e. Apart from once weekly methotrexate usage, there are still alternative dosing schemes (e.g. three divided doses over 24 or 36 hours, dosing 3 days a week). Please provide information on the number of cases of medication errors associated with alternative dosing schemes and discuss these cases.

f. Please provide information in tabular format on the daily dose used, cumulative dose used in period between error and event and the length of treatment prior to the error. Please provide information about the management of overdose of cases with inadvertent daily instead of weekly drug usage.

Question 3

Please provide and discuss relevant literature on inadvertent daily instead of weekly methotrexate usage (not reportable as ICSR). Please differentiate in the discussion between oral and parenteral formulation. Details on the search strategy should be provided.

Question 4

Please present the following information on the Risk Minimization Measures (RMMs) currently implemented for inadvertent daily instead of weekly usage of methotrexate: types of RMMs and dates of implementation (see table 2). Dates on implementation refer to the date when a certain RMM was actually implemented by an MAH/NCA in a country (e.g. date of dissemination of DHPC, date of implementation of SmPC update recommended by PRAC, date of launch of NCA communication campaign). For presentation of data for whole EEA, only EEA-wide RMMs should be presented along with the date of the recommendation. Additionally, details of RMM activities and their effectiveness should be briefly described for each country.

Please provide the information separately for oral and parenteral formulation as applicable.

Table 2: Risk minimisation measures per EEA member state

Member State	Type of RMM	Date of implementation

Question 5

Based on the review of all available data and taking into account results from root cause analyses, please provide proposals and justifications for routine and additional RMMs, which may prevent the inadvertent incorrect dosing of methotrexate products authorised in the EEA. In addition, proposals should be made how their effectiveness could be monitored? Please differentiate between oral and parenteral formulation.