MINISTERIO DE SANIDAD, SERVICIOS SOCIALES E IGUALDAD
agencia española de medicamentos y productos sanitarios

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NOTIFICATION TO THE PRAC OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC
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This notification is an official referral under Article 31 of Directive 2001/83/EC to the PRAC made by Spain-Agencia Española de Medicamentos y Productos Sanitarios (AEMPS)

Product Name (s) in the referring Member State if applicable	Products containing methotrexate oral formulations
Active substance (s) *Please clarify name(s)and total number(s) of active substance(s)*	Methotrexate
Pharmaceutical form(s) *If all pharmaceutical forms are included, stat "All".* *If not all pharmaceuticals forms are included, please specify the ones included.*	*Oral formulations*
Strenght(s) *If all strengths are included, state "All".* *If not all strengths are included, please specify the ones included.*	*All*
Route of administration(s)	*Oral use*
Applicants/Marketing Authorisation Holder(s) in the referring Member State	Wyeth, Cipla

Background

Oral methotrexate is authorised in the EU for daily or weekly administration, depending on the therapeutic indication. Serious cases, some of them fatal, caused by inadvertently taking the product daily instead of weekly dosing have been reported.

Several Member States have been taking a number of risk minimisation measures over the years. However, medication errors due to inadvertently taking the product daily instead of weekly, leading to overdose with serious consequences are still reported.

Within the recently assessed last periodic safety update report (PSUR) (covering data from 1st July 2014-30th June 2017), a number of adverse events related to overdose have been reported (as an example, one of the marketing authorisation holders reported 440 cases of adverse reactions due to inappropriate schedule of drug administration, 335 of them received from Germany, France, United Kingdom, Italy and Spain).

A recent search performed in EudraVigilance with the PT "inappropriate schedule of drug administration" revealed that the majority of cases where a route of administration was reported concerned oral use of administration.

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Based on the evaluation of PSUR data from MAHs, PRAC concluded on the need of some routine risk minimisation measures (RMMs) such as update of the product information and the inclusion of a visual reminder in the outer package (details to be agreed at national level). However, such measures have already previously been implemented in Spain, including a visual reminder in the outer package, very detailed information in SmPC and PL of the only product marketed in Spain until recently, and several communications on the issue. Despite these measures, medication errors with life-threatening outcomes are still occurring.

After PRAC discussion on further RMMs intended to prevent such medication errors, and reported experience from other MSs during the recent PSUR single assessment, PRAC concluded that a homogeneous approach should be implemented in all MSs and for all methotrexate containing medicinal products given orally that are indicated for weekly administration, regardless the authorisation procedure. To this end, the PRAC requested additional data analyses and consideration of further RMMs as well as means to measure their effectiveness to be presented by the MAHs at the time of the next PSUR for methotrexate.

However, Spain considers that there might be additional reasons for these medication errors than previously thought. In order to fully elucidate the root causes and to take appropriate measures to overcome this issue, data from other sources than PSURs, including information from National Competent Authorities, healthcare providers, and other stakeholders would be relevant. Spain, therefore, considers that, in order to protect public health, there is a need to initiate a referral procedure and for PRAC and CHMP to assess additional data and information that was not available to the Committees in the PSUR assessment procedure.

Based on the above, Spain considers that the issue should be thoroughly assessed based on data from all relevant sources in order to identify harmonised and appropriate risk minimisation measures to be implemented in all Member States and all products containing oral methrotrexate for indications that require weekly dosing, so that medication errors could be effectively prevented. Furthermore, in light of the seriousness of some of the cases of accidental overdosing, there is a need to initiate this assessment.

Issues to be considered

Having considered that medicinal products containing oral methotrexate for weekly administration are authorised in several Member States, Spain considers that it is in the interest of the Union to review data from all relevant sources in order to assess the need for additional measures aimed at minimising the serious risk for overdose toxicity as a consequence of daily intake instead of weekly intake. Although efforts are being taken as a consequence of the evaluation of the last available PSURs, considering the relevance of the topic, a further thorough review of the data and the risk minimisation measures that have been taken nationally over the last years is deemed necessary. This will allow the implementation of the most effective measures in a harmonised and timely manner so that this preventable and serious risk could be overcome.

In view of the above and the necessity to take an action al EU level, Spain understands it is in the interest of the Union to refer the matter to the Pharmacovigilance Risk Assessment Committee (PRAC) and requests that it gives its recommendation under Article 31 of Directive 2001/83/EC

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as to whether the marketing authorisations of these products should be maintained, varied, suspended or revoked.

As the procedure encompasses a centrally authorised product, pursuant to Article 31(1) of Directive 2001/83/EC the PRAC recommendation shall be referred to the Committee for Medicinal Products for Human Use to issue its opinion.

[redacted]

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