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Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

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

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

Jylamvo EMEA/H/A-31/1463/C/3756/0002

Nordimet EMEA/H/A-31/1463/C/3983/0006

INN: methotrexate

Note:

Assessment report as adopted by the PRAC and considered by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

| | |
|--|-----------|
| Table of contents | 2 |
| 1. Information on the procedure | 3 |
| 2. Scientific discussion | 3 |
| 2.1. Introduction..... | 3 |
| 2.2. Root cause analysis | 4 |
| 2.2.1. EudraVigilance case report analysis | 5 |
| 2.2.2. MAHs case report analysis | 5 |
| 2.2.3. Published literature..... | 7 |
| 2.2.4. Written consultation of healthcare professionals organisations..... | 12 |
| 2.2.5. Root causes analysis summary | 13 |
| 2.3. Stakeholders input | 14 |
| 2.4. Discussion on risk minimisation measures | 17 |
| 3. Risk management | 24 |
| 3.1. Risk management plan..... | 24 |
| 3.1.1. Pharmacovigilance activities..... | 24 |
| 3.1.2. Risk minimisation measures..... | 25 |
| 4. Recommendations and conclusions on benefit-risk | 27 |
| 5. Conditions to the marketing authorisations | 30 |
| 6. Grounds for recommendation | 31 |
| 7. References | 32 |

1. Information on the procedure

Methotrexate is authorised in the European Union since the 1960s and is used extensively. It is indicated in the treatment of cancers such as acute lymphoblastic leukaemia (ALL) and various inflammatory conditions, including rheumatoid arthritis, juvenile idiopathic arthritis, psoriasis, and psoriatic arthritis and as steroid sparing adjunctive therapy in Crohn's disease.

Each group of indications has a different administration schedule:

- For the treatment of cancer, various administration schedules including daily dosage may be used;
- For the treatment of autoimmune diseases, which require immunosuppressive therapy like rheumatoid arthritis, psoriasis, Crohn's disease and other autoimmune diseases, it is prescribed as a single low-dose, once a week.

Methotrexate-containing products are authorised in all EU Member States, and either oral or parenteral formulations or both pharmaceutical formulations are available.

Serious cases of overdose, sometimes fatal, have been reported in patients inadvertently receiving the product daily instead of weekly for indications that require weekly dosing. Despite additional risk minimisation measures having already been put in place, reports continued to be received.

On 22 March 2018 Spain therefore triggered a referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data, and requested PRAC to assess the root causes and the impact of the risk of medication errors on the benefit-risk balance of oral formulations of methotrexate and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

The PRAC further agreed during its April 2018 plenary meeting to extend the scope to include also parenteral formulations of methotrexate, in view of a number of cases reported with these formulations as well, and due to the fact that for a high number of cases reported as "incorrect schedule of dose administration" with methotrexate, the route of administration and the pharmaceutical form had not been specified.

2. Scientific discussion

2.1. Introduction

Methotrexate is a folate antimetabolite that inhibits DNA synthesis, repair, and cellular replication. Methotrexate irreversibly binds to and inhibits dihydrofolate reductase, inhibiting the formation of reduced folates, and thymidylate synthetase, resulting in inhibition of purine and thymidylic acid synthesis, thus interfering with DNA and RNA synthesis, repair, and cellular replication. Methotrexate is cell cycle specific for the S phase of the cycle. Actively proliferative tissues are more susceptible to the effects of methotrexate.

Methotrexate represents an essential component in the prophylaxis and treatment of CNS leukaemia in children and adults. Methotrexate is a vital component of many chemotherapy regimens for many types of potentially fatal cancers.

Although methotrexate was originally developed as a chemotherapeutic agent, in low doses it is approved for and commonly used in the treatment of certain autoimmune diseases such as rheumatoid arthritis, psoriasis and Crohn disease. Low-dose methotrexate belongs to the group of disease-modifying anti-rheumatic drugs (DMARDs). The mechanism of action for low-dose methotrexate as

DMARD remains to be fully elucidated. Multiple mechanisms, including but not limited to accumulation of adenosine, inhibition of T-cell activation and deactivation of enzymes relevant to immune system function, seem to be involved.

Methotrexate alone or in combination with other agents has become the standard of care for moderate to-severe rheumatoid arthritis. Among the conventional DMARDs, methotrexate remains first-line therapy for most children with juvenile idiopathic arthritis due to its long track record of safety and effectiveness in the management of peripheral arthritis. Furthermore, methotrexate is a backbone medication for the systemic treatment of psoriasis.

When used for treatment of psoriasis, initial methotrexate dose is recommended to be 10 to 25 mg per week; doses above 30 mg per week should not be exceeded. Methotrexate is usually administered in an intermittent low-dose regimen such as once weekly. Similar regimens are in use in patients with rheumatoid arthritis. The usual dose range is between 7.5 mg and 25 mg per week. For the treatment of Crohn's disease (CD), 25 mg/week is the standard induction dose. In oncology indications, various administration schedules including daily administration of medium (single dose 100-1000 mg/m²) to high doses of methotrexate may be used (single dose >1000 mg/m²).

Methotrexate for oral use is available in strengths ranging from 2.5 mg to 10 mg (tablets) and as a 2 mg/ml oral solution. Methotrexate is also available for parenteral use; individual doses (syringe, pen) range from 2.5 mg to 30 mg/1 to 30 syringes or pens per pack. The largest pack size contains 5000 mg (1 vial x 5000 mg).

Medication errors are an on-going issue with methotrexate use. Once daily instead of once weekly dosing of methotrexate leading to drug overdose is the most concerning, with more than a hundred cases of inadvertent once daily instead of once weekly dosing of oral methotrexate having been reported between 01 July 2014 and 30 June 2017 in the EU, of which at least 18 were fatal.

Clinical manifestations of methotrexate toxicity include nausea, vomiting, diarrhoea, mucositis, stomatitis, esophagitis, elevated hepatic enzymes, renal failure, rash, myelosuppression (leukopenia, pancytopenia, thrombocytopenia), acute lung injury, tachycardia, hypotension, and neurologic dysfunction (depression, headache, seizures, motor dysfunction, stroke-like symptoms, encephalopathy, coma). Toxic effects may occur hours to days to weeks after methotrexate administration or overdose. Because the toxicity of methotrexate is related to area under the curve of the plasma concentration–time curve, toxic effects are far more likely with large intravenous doses or inadvertent daily oral dosing, compared with a single acute overdose. In patients taking chronic low-dose methotrexate, treatment with folic acid is recommended to reduce risk of several common toxicities and the likelihood of treatment discontinuation.

To better understand the causes for this type of medication errors and recommend appropriate risk minimisation measures, the PRAC requested marketing authorisation holders to perform a root cause analysis based on the information available from case reports and literature data for both oral and parenteral formulations, as well as to discuss risk minimisation measures to address the risk. The PRAC also considered a EudraVigilance analysis performed by EMA and consulted national competent authorities and stakeholders to gather further information and their views on the matter.

2.2. Root cause analysis

In order to assess the root causes and the impact of the risk of medication errors due to inadvertent daily oral dosing instead of weekly dosing, the PRAC considered the analyses of cases report of inadvertent daily instead of weekly usage of methotrexate-containing products, including reports without adverse events, for the period 1 January 2013 until 31 March 2018 from the EudraVigilance

database as well as from the data provided by the MAHs of methotrexate-containing products. Data were also provided by healthcare professional organisations.

2.2.1. EudraVigilance case report analysis

EudraVigilance database was analysed by EMA for cases that describe 'medication error' terms with methotrexate. Out of a total of 785 cases with EEA origin, identified in EudraVigilance and retrieved with the SMQ Medication Errors (broad) in the period from 01 January 2013 to 31 March 2018, 146 cases (19%) were due to inadvertent daily instead of weekly usage. Of these, 144 were reported as serious with 29 fatal outcomes. Most cases were due to the use of oral formulations. These comprised a total number of 119 cases, of which 117 were reported as serious with 17 fatal outcomes. It should be noted that in 15 (all formulations) and 14 (oral formulations) cases, information on the outcome death was not available. In a total of 20 cases, the formulation used by the patient was unknown. Only 7 cases were attributed to the use of parenteral formulations, all of which were serious with 2 fatal outcomes.

Inadvertent daily instead of weekly usage of methotrexate was reported in EudraVigilance by a total of 17 EEA countries.

The analysis of cases in different age groups revealed that the majority of cases (82 in total) occurred in patients who were 65 years and older. Thirty-six cases occurred in 19 – 64-year-old patients and in 28 cases information on age was missing. Of note, the highest number of fatalities was noted in patients older than 75 years of age.

The daily dose taken by patients was reported to range from 2.5 mg to 160 mg with a mean and median dose of 11.8 mg and 10 mg, respectively. Information on the daily dose was missing in 26 cases. The reported duration of daily intake ranged from 1 to 1095 days with a mean and median of 18 days and 8 days, respectively. Information on the duration of daily intake was missing in 27 cases.

Cases were further analysed by PRAC in order to identify the root causes for medication errors. It was noted that many cases lacked relevant information on the root cause leading to the medication error. Nonetheless, analysis of cases which did contain relevant information revealed that errors occurred at all stages of the medication process. Several root causes were identified, including switch to new formulation; use of the wrong dose schedule by the patient despite clear instructions from the rheumatologist; mix-up of dose schedules between methotrexate (weekly schedule) and another medication (daily schedule) taken at the same time, leading to the patient taking methotrexate daily and the other drug weekly; failure by patient to understand the posology; prescription of wrong dosing schedule by physician; error by nurse when distributing medications; error in transcription from treatment at home into admission report in hospital; misunderstanding of prescription by pharmacist; self-medication and self-directed dose increase by patient who had received methotrexate in the past; lack of clarity in prescription; mix-up of medications at physician level; error in dispensing; incorrect prescription due to incorrect dictation in medical record; errors in dosing; lack of feedback between the patient and the clinician; patient's impaired cognition; concomitant drug administration; impaired renal function; old age.

2.2.2. MAHs case report analysis

The MAHs of methotrexate-containing medicinal products evaluated a total of 361 case reports for error sources, how the error was detected, indication and specific characteristics or healthcare system that could have contributed to the error. It should be noted that some case reports may have been duplicates and that several cases were of poor quality with only scarce information provided. A quantitative assessment could therefore not be performed.

Overdoses with methotrexate typically led to haematopoietic and gastrointestinal side effects, such as pancytopenia, thrombocytopenia, leukopenia, neutropenia, mucositis, stomatitis and abdominal pain. Additionally, several skin reactions as skin necrosis, skin ulcer, skin exfoliation and erythema were reported.

Analyses showed that in the majority of the reported cases with inadvertent daily instead of weekly use, methotrexate was prescribed for non-oncological indications, and most commonly for rheumatoid arthritis. However, in 30-40% of the reported cases, no data about indication was presented, so no firm conclusion can be drawn.

Fewer cases occurred with methotrexate parenteral formulations than with oral formulations and they were detected sooner.

An analysis of the daily doses reported in the cases showed that doses ranged from 2.5 mg to 160 mg. Although in the majority of the cases, dose was not reported, commonly reported doses were 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg and 25 mg.

In cases of parenteral daily intake, methotrexate overdose was detected earliest after two to four days, while oral overdoses were earliest detected after five days.

In general, cases reported that medication errors with methotrexate regarding inadvertent daily instead of weekly use were discovered after 4-7 days, 2-4 weeks, 2-3 months or one year. However, there were a few cases where medication error with methotrexate was discovered after more than 10 years (12, 17 and 30 years). Details were not provided so it was not possible to assess whether patients took methotrexate daily all this time or if this was the total length of their treatment with methotrexate. Analysis also showed that medication errors with methotrexate due to daily usage occurred mainly in first time users.

The case numbers stratified by age point towards a trend of higher cases in older patients (>65 years).

MAHs observed that in most cases, medication error with methotrexate was discovered by physicians due to the reported adverse drug reactions (ADRs) and hospitalisation of the patients or in the context of a regular patient examination. Pharmacists also discovered medication errors, either upon the review of prescriptions or because patients came too soon for another pack. In a very small number of reported cases, patients' family or patients themselves discovered medication error by reading instructions written on the package of methotrexate or upon review of the package leaflet. Cases of inadvertent daily instead of weekly use of methotrexate were observed in clinical studies as well.

The stage of medication process where the error occurred the most commonly was the drug administration stage. These errors were due to misunderstanding of the prescriptions, misunderstanding of the language, non-compliance followed by overcompensation of missed doses, administration of methotrexate instead of other drug and accidental overdoses. One of the MAHs specifically reported about the significant number of cases in their safety database in which patients took methotrexate daily by mistake instead of folic acid. The main cause for the administration error in these cases was the confusion between methotrexate and folic acid tablets. Furthermore, patients received an excessive quantity of methotrexate tablets at the pharmacy, allowing a daily administration of methotrexate.

Possible contributing factors for dosing errors with oral methotrexate included patients' advanced age, concomitant polypharmacy, recent treatment initiation, missing training for drug administration, recent methotrexate dosage change (e.g. switch from another daily administered medication for the same indication to the weekly administered drug methotrexate), patient memory loss/ confusion, as well as co-prescription of folic acid with specific scheme of administration and concomitant medication with daily dosing schedule. Patients' medical history was notable for advanced age, multiple morbidities and

concomitant polypharmacy that is associated with well-known increased risk of medication error, poor adherence and ADRs.

Other reported stages of medication errors involved prescribing errors, administration errors by healthcare professionals, and dispensing errors.

Prescribing errors occurred upon patients' admission, patients' discharge or transition of patient care, that are well-known risk situations for medication errors. They included in particular: incorrectly prescribed schedule of drug administration, and incorrectly transcribed prescriptions. Possible contributing factors for prescribing errors in these cases included medicines transcription upon patients' transfer of care, co-prescription of concomitant medication with daily dosing schedule and prescription of methotrexate treatment by hospital physicians who are not used to once-weekly dosing schedule of methotrexate (e.g. on wards for surgery, geriatrics, in rehabilitation hospitals).

Possible contributing factors for reported administration errors by healthcare professionals included the delivery of medical prescriptions with confusing/unclear instructions (e.g. incomplete prescriptions by missing notification of weekly dosage), the use of abbreviations in computer-assisted prescription (e.g. only "M" was stated which the healthcare professional (HCP) read as "morning" instead of "Monday"), the dispensing of excessive quantities of methotrexate tablets by the hospital pharmacy, and possible lack of knowledge of hospital HCP regarding once-weekly dosing schedule. Furthermore, high workload with staff under time and pressure, and writing the explicit recommendation of daily usage on the package although weekly dosage was prescribed on prescription were also reported.

Contributing factors for dispensing errors included possible lack of knowledge of once-weekly dosing schedule of methotrexate.

2.2.3. Published literature

Overall, 121 literature references were provided by the MAHs. Most references (n=60) described case report/reports (including cases reportable as ICSR and cases not reportable as ICSR). Publishing dates of case reports were between 1985 and 2018. The origin of most cases was US (n=12) followed by India (n=7), UK (n=5), Australia (n=4) and Germany (n=4).

The relevant literature data is presented below, with special focus on root-cause analysis and recommendations for prevention of medication errors.

Cairns and colleagues (2016)[5] investigated methotrexate dosing errors reported to the National Coronial Information System (NCIS), the Therapeutic Goods Administration Database of Adverse Event Notifications (TGA DAEN) and Australian Poisons Information Centres (PICs). A retrospective review of coronial cases in the NCIS (2000-2014), and of reports to the TGA DAEN (2004-2014) and Australian PICs (2004-2015) was performed. Cases were included if dosing errors were accidental, with evidence of daily dosing on at least 3 consecutive days.

Twenty-two deaths linked with methotrexate were identified in the NCIS, including seven cases in which erroneous daily dosing was documented. Dosing errors were recorded in seven cases (five men, two women); methotrexate had been taken for 3 to 10 consecutive days. One further patient deceased after taking more than the prescribed dose of methotrexate (based on tablets remaining and dispensing date) was not included because consecutive daily dosing was not conclusively established. Abnormal blood cell counts were documented for all seven deaths linked with dosing errors (median age, 78 years; range, 66-87years). Reasons for the errors included dosette packaging errors by pharmacists (3 cases), prescribing error (1), mistaking methotrexate for another medication (1), dosing error by carer (1), and prescriber patient miscommunication (1). The TGA DAEN included 16 reports of methotrexate-related adverse events meeting the search criteria, including five deaths.

These were reviewed for inclusion, and unintended daily dosing was documented in ten cases (median age, 58 years; IQR, 42-74 years; range, 41-85 years; eight women), including two deaths (two women, aged 71 and 83 years). The PIC dataset contained 92 cases of methotrexate-related medication error meeting inclusion criteria. Between 2005 and 2013, the annual number of events was fairly stable (four to nine cases per year). There was an increase during 2014-2015 (16 and 13 cases respectively). PIC exposures with prescribing and dispensing habits were compared. Most methotrexate was dispensed in 10mgX50 tablet packs, the rate of dispensing of which increased steadily during the study. The rate of dispensing of the smaller pack size (10mgX15), introduced in 2008, has grown, but has not reached that of the larger pack size, which still accounted for 47% of scripts (and 79% of 10mg doses) in 2014. In the PIC dataset, exact ages were recorded in 51% of cases (median age, 65 years; IQR, 52-77 years; range, 28-91 years); at least 18 patients were over 75 years of age. Fifty-five of the 92 patients were women; sex was not recorded in seven cases. Call records documented a range of symptoms, including stomatitis, vomiting, reduced blood cell count and fever. The median number of consecutive days for which methotrexate was taken was 5 (IQR, 4-9 days; range, 3-180 days); the distribution was skewed, with 20 cases involving methotrexate taken for 3 consecutive days. The median daily dose taken was 10 mg (IQR, 10-15 mg; range, 2.5-60 mg). Where documented, reasons for errors in the PIC dataset included mistaking methotrexate for another medication (11 cases), often folic acid (6) or prednisone (4); carer or nursing home error (5); methotrexate being newly prescribed for the patient (5); dosette packing errors by the pharmacy (4); misunderstanding instructions given by the doctor or pharmacist (2); the patient believing it would improve efficacy (2); prescribing error (1); and dispensing or labelling error (1).

Moore and colleagues (2004)[19] analysed all adverse-event reports submitted to FDA between November 1997 and December 2001 indicating potential medication errors involving methotrexate to determine indication for use, the type of error, and the point in the medication-use process where the error occurred. A total of 106 cases of reported medication errors associated with methotrexate were identified, including errors resulting in 25 deaths (24%) and 48 other serious outcomes (45%). The most common types of errors involved confusion about the once-weekly dosage schedule (30%) and potential for confusion in these error cases was increased by polypharmacy; 73% of the patients were taking 2 or more drugs (mean, 3.5 drugs). Errors in consuming evolved primarily out of patient confusion about the weekly dosage schedule (17/21 cases).

Perregaard and colleagues (2015)[20] analysed databases for cases involving low dose methotrexate 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). They categorised the place where the error occurred, the processes and types of error involved the person responsible, and the clinical outcome. 173 errors were identified. Prescription errors involving daily rather than weekly administration, by hospital physicians, were most likely to result in serious outcomes, including deaths. The error mechanism was evaluated in 129 events. Action-based errors comprised 50 % and knowledge-based errors 34 %. Action based errors were more likely to result in completed errors, whereas knowledge-based errors more often resulted in near misses. 53 (31 %) involved incorrect daily administration (near miss= 18, mild=3, moderate=4, severe=10, death=4, unknown =14).

Salgueiro-Vazquez and colleagues (2017)[22] analysed spontaneous reporting of errors associated with oral methotrexate treatment registered in the SEFV-H database (Spanish Pharmacovigilance Adverse Event Data [FEDRA®]) from 01.01.1982 until 18.02.2016. High level group terms of the Medical Dictionary for Regulatory Activities were searched for: "medication errors" or "overdose" or "problems associated with the use of products". 47 of the 61 spontaneously reported medication errors associated with oral methotrexate identified. 25 cases were excluded, 14 of them because of errors

related to methotrexate administered by routes other than oral (n = 3, 2 subcutaneously and one intravenously). Eleven of the registered notifications to FEDRA correspond to cases published in the medical literature. Age, median and range, of the patients was 69.5 (30-88) years. 59.6% (n = 28) were women. All cases were severe and 6 of them fatal. In most cases medication process affected was administration or consumption (68.1%) followed by prescription (19.1%) and dispensation (8.5%). Area in which the error occurred was non – hospital in most cases (n=32, 68.1%), out of which most were related to patients (n=25). In cases of error in the daily regimen rather than weekly, the average length \pm SEM of treatment with methotrexate (n = 23) was 13.74 \pm 2.2 days, mean cumulative dose \pm SEM (n = 24) 277.3 \pm 142.0 mg. It accounted for 74.5% of the errors in this study compared with 31% in Perregaard and colleagues (2015) and 30% in Moore and colleagues (2004).

Schicchi and colleagues (2017)[23] retrospectively analysed all cases of methotrexate overdose due to therapeutic error in non-oncology patients referred to a Poison Control Centre in Pavia, Italy, during 8 years (June 2007 to June 2016). Overall 35 cases were included (50% male), aged between 17 and 86 years. In 5 cases patients were nursing mothers (not in treatment) to which methotrexate was wrongly sold by the pharmacist instead of methylergometrine. The remaining 30 cases involved patients who had been prescribed methotrexate for the first time for an autoimmune/rheumatic disease. In 27 cases the wrong dose was prescribed, in 2 cases methotrexate was administered in an incorrect way, and in 1 case, it was administered despite the patient having severe renal failure. In all the cases where the dose was incorrect, the weekly prescribed dose (range 2.5–12.5 mg/week) was taken daily (17.5–87.5 mg/week); this mistake was recognized after a period ranging from 2 to 21 days. Clinical manifestations were characterized by mucositis (14/35), myelosuppression (12/ 35), asthenia (6/35), acute renal failure (5/35), diarrhea (4/35), vomiting (4/35), headache (2/35) and hepatitis (2/35). All patients were treated with calcium levofolinate and forced alkaline diuresis. N-acetylcysteine was administered in 2 patients with hepatitis, and growth-factors in one patient. Methotrexate plasma concentrations were available for 6 patients, and were within the therapeutic range.

Stuerzebecher and colleagues (2015) [26] described 94 exposures to methotrexate reported to Poisons Information Centre Erfurt in Germany in period between September 2000 and August 2014. Of these cases, 24 (25.5%) were suicide attempts, 14 (14.9%) were accidental ingestions (mostly by children) and in 19 cases (20.2%) adverse events at therapeutic doses had occurred. Medication errors were observed in 37 cases (39.4%), of which one third (n =13) occurred in hospitals or care homes, and two-thirds (n=24) at home. In 14 cases, daily application of a weekly dose of methotrexate for 4 to 21 days resulted in pancytopenia and mucositis, with one fatality. Since 2010, methotrexate is the standard treatment option for rheumatoid arthritis in Germany and is therefore widely used. Despite warnings by the German Federal Institute for Drugs and Medical Devices (BfARM) concerning correct dosage and overdose, medication errors both by patients and by hospital staff are common. Doses exceeding the recommended daily dose can lead to severe symptoms and even death.

Vial and colleagues (2014) [30] described cases involving an oral formulation of low-dose methotrexate and collected by the French network of poison control centres or pharmacovigilance centers from 2007 to October 2013. Cases were included if any of the following conditions were fulfilled: (1) intake of more than 2-fold the intended weekly dose, (2) a weekly cumulative dose higher than 30 mg, or (3) an error repeated for more than 7 consecutive days. A follow-up at least 4 days after the last methotrexate dose was also required in asymptomatic patients. The severity of symptoms was classified according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03. 73 cases (54 females, median age: 76 years) were retained. The error occurred at home in 43 cases and in hospital or health care service in 28, and 16 resulted from a prescription error. Intake of methotrexate daily instead of weekly was the most common (89%). The median duration of the error was 8 days (1–90 days). The median ingested dose was 7-fold (1.3–20) the intended dose and the median cumulative dose mistakenly received was 80

mg (20–300). The medication error was identified from symptoms suggestive of methotrexate toxicity in 67% of patients. Only 11 patients remained asymptomatic on follow-up. Among the 62 patients who developed complications attributable to methotrexate, 14 experienced minor symptoms and 47 had severe (grade 3) complications, with oral mucositis and cytopenias as the most common. Overall, 9 patients died.

Additional search of literature identified an article from Attalla and colleagues (2018)[2], “Methotrexate- Incorrect drug administration rate” in Signal publication issued by Uppsala Monitoring Centre. In VigiBase 24 cases reported incorrect drug administration rate of methotrexate between 2009 and January 2018. Thirteen cases were from France, three from Bulgaria, three from USA, and each from Denmark, Germany, Spain, Switzerland and UK. The patient age ranged from 3 to 92 years, with median age of 63 years, based on the 21 reports where age was provided. Men accounted for 15 and woman for 9 reports. The indications for treatment were reported as psoriasis in three cases, rheumatoid arthritis in three cases, various cancers in three cases, bullous pemphigoid in one case and asthma in another case. In remaining 13 cases, the indication was unspecified. Methotrexate was administered intravenously in five cases and orally in 19 cases. In the cases where oral methotrexate was prescribed, the patients had taken it daily instead of weekly. In one case, a prescription error was reported. However, in most cases it appears that the patient did not understand that methotrexate was to be taken weekly and not daily. In addition to errors in administration, other reactions were reported. The five most reported reactions included mouth ulceration (4), thrombocytopenia (4), gastritis (4), pancytopenia (3) and pharyngitis (3). The outcome was recovered in 15 cases, not recovered in one case and unknown in another case. In the remaining two cases, the patient died. Patient information states that methotrexate is to be taken weekly. However, these reports show that the patient took it daily instead with significant adverse effect. The dosing instructions was considered to be particularly confusing in the cases where the weekly dose is divided into three doses to be taken within 24 hours, with 12-hours gap between each dose. The authors were of the view that clearer instructions both in SmPC and by the prescriber are necessary, and that the patient has understood how medication needs to be taken .

Other literature references are presented below per cause of medication errors (if available):

- Confusion by healthcare professionals

In study by Karch (2003)[16], a physician inadvertently wrote methotrexate dosing as 15 mg/d oral use, and fell into the routine of prescribing daily doses (he had written 18 different prescriptions that day). Since methotrexate may be given daily as an antineoplastic, the pharmacist who filled the prescription did not detect the error.

Gaunt (2016)[12] describes a case where a pharmacy label was typed incorrectly with directions to “Take 4 tablets once daily for 7 days instead of 10 mg weekly (i.e. 4 tablets once every 7 days). Although the 80-year old patient was advised about the correct dosing regimen by the physician, the patient followed the instructions on the label, assuming she misunderstood the physician.

- Methotrexate mistaken for another medication

Cairns (2016)[5] describes 11 cases of mistaking methotrexate for another medication (11 cases), often folic acid (six cases). Chatterjee (2004)[7] also mentions the similar appearance of methotrexate and folic acid 5mg tablets, which are often prescribed to the same patient, that leads to mix-ups.

- Misinterpretation of the directions (“morning” instead of every “Monday”)

Blinova (2008)[3] describes a case where a patient misread the directions on a prescription bottle and took 10 mg every “morning” instead of every “Monday”.

- Confusion related to divided doses

ISMP Canada describes a case of adult patient who had been receiving methotrexate for rheumatoid arthritis - the weekly dose was divided for three times weekly administration. The family physician inadvertently wrote a repeat prescription for methotrexate to be taken 3 times per day instead of dividing the weekly dose into 3 doses given at 12- hour intervals, i.e., over a 24-hour period, once a week (Grissinger M, 2018)[14]. Blinova (2008)[3] describes a patient that took methotrexate 2.5 mg every 12 h for 6 consecutive days, instead of 2.5 mg every 12 h for 3 doses each week. Arnet (2012)[1] describes a patient that had failed to correctly interpret the written prescribed schedule of three doses at 12-h intervals weekly.

- Prescribing error

Moisa (2006) [18] describes series of four cases of fatal methotrexate intoxication due to medical malpractice. Sinicina (2005) [25] describes a case of 74-year-old woman with rheumatoid arthritis (RA) that was admitted to the department of vascular surgery of a teaching hospital. Her internist listed her medicine for hospital doctors, intending a weekly dose "currently methotrexate 10 mg." A state employed nurse in the surgical department, inexperienced in methotrexate use for RA therapy, interpreted this order as "methotrexate 10 mg 1-0-0." The attending surgeons had only occasionally dealt with patients with methotrexate medication due to RA and thus did not question the dosage. The patient herself trusted the doctors and assumed that the change in methotrexate medication was necessary, since her medication was almost completely replaced by generics and she also received additional medication. Thus, she received an intended weekly dose of 10 mg daily for 9 days (total dose 90 mg over 9 days; intended dose 10 mg weekly). The patient died of pneumonia one week after the last methotrexate dose.

Declercq (2010) [11] reports a case of fatal medication error. After medication reconciliation, the clinical pharmacist communicated to the surgeon the patient's methotrexate posology, indication and risks. However, during the 1.5 week pharmacist's absence and despite the written information in the computerized physician order entry (CPOE), methotrexate was incorrectly prescribed and as a result, 35 mg was administered in 7 days, i.e. a fivefold overdose.

Caridad (2013) [6] describes cases from literature where it was revealed that prescription error was made by physicians not treating disease for which methotrexate was prescribed.

- Self-administration by patients

Troeltzsch (2013) [28] describes a patient who had been recently prescribed to treat her RA. The patient was informed that her mucosal lesions were consistent with MTX toxicity, after which she admitted difficulty adhering to the recommended MTX dosing and schedule. After initially missing doses of the new medication, she had overcompensated for her non-compliance and had taken MTX 15 mg once daily for the last 10 days.

Skusa de Torre Ataíde (2003) [27] describes cutaneous adverse effects of high dose methotrexate in psoriasis. A patient had been using 12.5 mg methotrexate per week when, seeking faster improvement, he made use of 75 mg in four days' time.

Cohen (2002)[9] describes a patient taking extra doses of methotrexate as needed to relieve arthritic symptoms.

- Computer systems issues

Van den Bemt (2009) [29] states that transcription errors (both by nurses and pharmacy technicians) when entering the prescription into the pharmacy computer) also occur. It is described that pharmacy computers in The Netherlands in general have very good alerting systems for overdosing, but most systems cannot handle once weekly dosing, which is the second problem.

Chatterjee (2004)[7] states that computer errors had also led to the 'once daily' option being selected on dispensing information for patients - when oral methotrexate is one of only six medicines in the British National Formulary that should be taken weekly rather than daily.

- Using of Dosette box

Brown (1991)[4] and Cairns (2016)[5] describe errors in filling of dosette box as a cause of wrong methotrexate administration leading to sequential use.

- Initiation of therapy

In study done by Salgueiro-Vazquez (2017)[22] the average length \pm SEM of treatment with methotrexate (n = 23) was 13.74 \pm 2.2 days (with mean cumulative dose \pm SEM (n = 24) 277.3 \pm 142.0 mg) clearly indicating the start of the therapy as a crucial point for prevention of methotrexate medication errors.

- Large packaging

Arnet and colleagues (2012)[1] detected the following error: the packaging supplied 25 weeks (or 6-months) worth at a weekly intake of four tablets, but would only last for 25 days when taken daily. Because the next physician visit was scheduled 21 days later, the pack size could have erroneously led the patient to believe that the control visit date had been selected to coincide with reaching the end of the pack. The authors considered that the solution here would be an appeal to manufacturers to release a smaller package size of methotrexate into the market to reduce such risks and to physicians to prescribe smaller quantities.

In a study by Vial (2014)[30] the median duration of the methotrexate daily instead of weekly intake was 8 days (1–90 days) while the median ingested dose was 7-fold (1.3–20) and the median cumulative dose mistakenly received was 80 mg (20–300).

In the study performed by Stuerzebecher and colleagues (2015) [26], daily application of a weekly dose of methotrexate for 4 to 21 days resulted in pancytopenia and mucositis in 14 cases, with one fatality.

In the study performed by Schicchi and colleagues (2017)[23], in all cases where an incorrect dose had been prescribed, the weekly prescribed dose (range 2.5–12.5 mg/week) was taken daily (17.5–87.5 mg/week); this mistake was recognized after a period ranging from 2 to 21 days.

In the study by Salgueiro-Vazquez (2017) [22], in cases of error in the daily regimen rather than weekly, the average length \pm SEM of treatment with methotrexate (n = 23) was 13.74 \pm 2.2 days, mean cumulative dose \pm SEM (n = 24) 277.3 \pm 142.0 mg.

- Elderly patients

Kanagarajah (2000) [17] states that factors such as sensory and cognitive impairment may increase the chance of patient-related errors. In one of the cases, there was clearly a misunderstanding of the mechanism of effect of methotrexate as it was used for symptom relief. The drug is renally cleared and may therefore accumulate in the older patient with reduced renal function (Christensen *et al.*, 2013 [08]).

2.2.4. Written consultation of healthcare professionals organisations

The PRAC also liaised with relevant healthcare professional organisations at the start of the review and asked them to share any data they would have concerning the root-causes for medication errors due to daily instead of weekly administration and on the implementation of risk minimisation activities aimed at preventing this medication error.

A number of causes for medication errors were highlighted by the HCP organisations:

- Ambiguity of the product information due to the different indications and dosing schedules authorised for methotrexate-containing medicinal products;
- Availability of large pack-size leading to repackaging with resultant loss of warning from manufacturers package and bearing the risk of massive uptake; confusion due to packaging in 28-day pack-sizes which are normally used for products requiring daily intake; difficulty to keep track/count of the number of tablets in bottles and for both the patients and caregivers to notice the error;
- Absence of warnings alerting on the once weekly dosing schedule on the outer packaging or warnings be covered by a label;
- Confusion due to unusual dosing regimen, division of the once weekly dose in 3 doses every 12 hours or up to five times a week, identification incidents due to the similarity of appearance of folic acid and methotrexate that are often taken concurrently, mix up with other products; inadequate awareness by HCPs;
- Errors in hospital, centre of convalescence or nursing home due to lack of knowledge, especially on non-internal-medicine wards (e.g. surgery, orthopaedics, geriatrician, resting homes, rehabilitation hospitals) not familiar with the use of methotrexate in rheumatologic indication (weekly administration, total doses and symptoms of intoxication);
- Communication issues in particular in a context of transition of care;
- Prescription errors or lack of clarify of the prescription; transcription errors of prescriptions or in patient record (e.g. on hospital admission);
- Electronic prescribing tools lacking features, e.g. missing notification of weekly dosage, no clinical decision support and warnings / defaults alerting systems for overdosing; systems not handling once weekly dosing; repeat prescribing without regular monitoring; dual therapy or too frequent repeat allowed; use of abbreviations; pick list showing first three letters only);
- Misunderstanding of prescription by pharmacist; dispensing in bottles;
- Lack of knowledge of patients and caregivers: misunderstanding of the dosing schedule; mix-up with other medication requiring daily intake; cognitive deterioration; patient family member gives medication; intake by the wrong patient.

2.2.5. Root causes analysis summary

Despite known limitations of e.g. spontaneously reported post-marketing case databases, analysis of all different sources of data (database, literature, HCP organisations) revealed that cases of medication errors can occur at all stages of the medication process, from prescription to administration.

Amongst the reported causes of medication errors were the ambiguity due to the product being authorised in different indications with different dosing schedules and the lack of clear and visible warnings alerting on the once weekly dosing schedule on the packs. Medication errors were also associated with the use of large packaging making it difficult to keep track/count of the number of tablets in bottles and for both the patients and caregivers to notice the error. In addition, it was noted that bulk packaging led to repackaging with resultant loss of warning from manufacturer's package and bearing the risk of massive accidental ingestion.

Medication errors due to errors in prescriptions were also reported. These included prescribing of wrong administration schedule, unclear instructions, or incorrect prescription due to incorrect dictation in medical record. Some errors were also due to the electronic prescribing tools lacking certain functions.

A lack of communication between patient/physician, physician/physician, physician/nurse or lack of feedback between patient and clinician also led to medication errors, in particular in a context of transfer of care. In hospital, rehabilitation facilities or nursing home, lack of communication and lack of knowledge about the once weekly dosing schedule of methotrexate for the treatment of autoimmune diseases led to transcriptions errors on prescriptions or in patient records, dispensing of excessive quantities of methotrexate tablets by the hospital pharmacy or administration errors by nurses.

Dispensing errors were also reported due to misunderstanding or misinterpretation of the prescription by the pharmacist or the filling of dosette box leading to sequential use.

A number of cases reported administration errors. These could be explained by the patient not given sufficient information by their physician, a lack of knowledge in patients and caregivers leading to misunderstanding / misinterpretation of the dosing instructions, self-medication and self-directed dose increase by patients who had received methotrexate in the past, switch from another daily administered drug to weekly administered methotrexate for the same indication, mix-up of dose schedules between methotrexate (weekly schedule) and another medication (daily schedule) taken at the same time, cognitive deterioration, methotrexate wrongly used for symptom relief, identification incidents due to similarity of appearance of folic acid (often taken concurrently), or division of the once weekly dose in several intakes to increase tolerability.

2.3. Stakeholders input

Written consultations

- Member states

At the start of the review the PRAC requested all MSs whether they had performed any root cause analyses of medication error reports and had taken any subsequent actions taken (risk minimisation measures besides update of product information). Also, they were asked to provide any recommendations or guidance regarding this topic, if available, and results of measurement of effectiveness if performed. The MSs have confirmed that in order to minimise risks associated with daily instead of weekly usage of methotrexate, they had mostly updated the product information. Other actions such as the dissemination of direct healthcare professional communications, publications in the literature or on websites have also been taken in some MSs. Depending on the national health systems, some MSs have also implemented changes to prescribing/dispensing computer software programs.

- Healthcare professional organisations

At the same time, the PRAC also liaised with relevant healthcare professional organisations and asked them to share any data they would have concerning the root-causes for medication errors due to daily instead of weekly administration and on the implementation of risk minimisation activities aimed at preventing this medication error.

As described in the section 2.2.4 of this report, the feedback received confirmed that medication errors can occur on all levels, from prescribing to administration, in hospital or in outpatient setting.

Other than the apparent mistakes made by patients or healthcare professionals due to the fact that the vast majority of drugs are taken once daily, the feedback received was that medication errors also occur due to poor communication between outpatient and inpatient setting, poor communication between HCPs and patients, poor communication between different wards in the same hospital, lack of knowledge, similarity in appearance of methotrexate and folic acid tablets, or inappropriate package size for the indication requiring once weekly dosing.

Suggestions for risk minimisation measures included a re-design of prescribing/dispensing software programs to default to a weekly (rather than daily) dosing schedule for oral methotrexate orders with hard stop verification; reduction of the number of tablets in the packs; limitation of the dispensation to a 4-week supply at a time and preferably of low-dose methotrexate if prescribed for indications requiring a once weekly dosing; ensuring that the appearance of methotrexate tablets is different to the one of the folic acid tablets; parenteral use to be preferred in patients prone to medication errors; development of a guidance for the treating specialist and/or family doctor; renaming of the products to better distinguish those to be taken/used weekly from those to be taken/used daily; inclusion of the qualifier 'weekly' in the name of the products intended for weekly use.

Stakeholder meeting

A stakeholder meeting was convened on 26 February 2019 to discuss the issues regarding cases of inadvertent overdose due to "daily" instead of "weekly" use and possible risk minimisation measures that could be implemented. This meeting was attended by representatives of a number of patients' and healthcare professionals' organisations, representing physicians, pharmacists or nurses experienced with the use of methotrexate, mainly in non-oncology indications.

The participants were asked for their views on any advantages/disadvantages of having tablets available in blisters rather than in bottles and although potential challenges with blisters for some patient groups were acknowledged, in particular patients having difficulties with manual handling, the majority of the group supported the use of blisters over bottles as inner packaging for methotrexate tablets. Indeed, similar challenges could be experienced with the use of bottles (e.g. child-resistant cap) but in addition, because of the difficulty tracing the number of tablets already administered, and other potential issues emerging from the repackaging of tablets from bottles (e.g. loss of leaflet and information on the inner/outer packaging, potential risk of cross-contamination, cytotoxicity of methotrexate), the group was of the view that bottles should not be used for methotrexate tablets and it was recommended that bottles are no longer marketed. One participant however considered that the risk of medication errors would not be mitigated by the use of blisters rather than bottles and highlighted that any measure taken should be risk-proportionate. Participants also commented that the packaging should be developed taking into account the characteristics of the targeted patient population. A suggestion was made that user testing should be performed to ensure that the blisters design meets patients' needs and takes into account any physical disabilities. Even though packaging of tablets in blisters was considered an important element for minimising the risk of dose errors with methotrexate, the group stressed that the implementation of this measure alone would not be sufficient and further measures to improve packaging and labelling need to be considered. The role of healthcare professionals in the communication of the dosing schedule was considered key and it was suggested that further training should be provided to HCPs who prescribe, dispense or administer these medicines. Another aspect highlighted was the potential for confusion of methotrexate tablets with folic acid tablets as these medicines are often co-prescribed and the tablets look similar.

The participants were also asked about the prescription process when methotrexate is used for the treatment of non-oncological diseases. It emerged from the discussions that the prescribing and dispensing patterns vary amongst practices and national healthcare systems (for instance prescriptions

can cover periods between 1 month and 1 year, depending on whether it is an initial prescription, and dispensations range from 1 to 3 months' worth of treatment). The group made a very clear distinction between prescribing and dispensing. Regarding the prescription duration, the group was generally of the view that no further restriction should be considered as patients may need the medicine for long-term use. It was emphasised that methotrexate should preferably be first prescribed by physicians with in depth knowledge of these medicines before any transfer to primary care. Restriction should be however applied when dispensing methotrexate. Limit dispensing the medicine to one month's worth of treatment was strongly recommended by some stakeholders. However some concerns were expressed that this could overburden patients in view of the long-term nature of the conditions. The characteristics of the national health system should also be taken into account. The group also made a call for prescribing and dispensing software programs to be improved to ensure that information about the correct posology and risk of medication error are well communicated to physicians and pharmacists and include pop-ups or reminders to further strengthen the process.

Reducing pack-sizes was considered by most as an essential measure to mitigate the risk of medication errors. However in view of the variety of strengths available and required doses (e.g. titration needed), no clear proposal on the optimal pack-size could be agreed upon. It was nevertheless suggested to avoid a 30 tablet pack-size which is a standard pack-size for a months' worth of daily intake which could lead to further medication errors. Regarding the strength, participants mentioned that in some Member States, only the 2.5 mg strength is available. Although it was acknowledged that the number of tablets at each intake may be high, limiting the availability of methotrexate to the lowest strength (2.5 mg) was unanimously supported by participants as a measure to minimise the risk of overdose.

The group also acknowledged that a substantial measure to consider for minimising the risk of errors would be to market two different medicines for oncology and non-oncology indications (with different names, different packaging, different indication and package leaflets etc.). In this way, it was proposed to have a specific and well-designed package for non-oncological use aiming at avoiding the risk of confusion and help patients to take the proper dose of methotrexate weekly. One expert suggested that the ideal product for non-oncological use should come in weekly individual dose packs and the package should contain 4 dose packs for a 4-week period. It was explained that two different medicines for oncology and non-oncology indications with different names, different packaging would imply the registration of a new marketing authorisation and a variation of the existing ones. The group was nevertheless of the view that having the PRAC's acknowledgment that such measure would be expected to largely reduce the risk of errors would send the right message, and that companies should be strongly encouraged to move in that direction.

The group also discussed the division of the weekly dose in multiple intakes (commonly 2 or 3 intakes *per* 24 hrs) as a possible measure to reduce the gastrointestinal adverse events associated with methotrexate treatment. Participants were however not aware of any robust supportive evidence for such a recommendation and could not identify a patient group for whom benefits of dividing the dose would outweigh the risk of medication errors. It was also highlighted that alternative measures such as switching from an oral to a sub-cutaneous formulation or increasing the dose of folic acid or ondansetron could be considered to mitigate the risk of gastrointestinal adverse events. In this context, it was mentioned that dosing of folic acid varies considerably across different practices and countries and that its use / dosing may not be based on evidence. One participant pointed however to feasibility aspects related to manipulation of sub-cutaneous formulations in clinical practice and direct administration by patients. Overall, it was agreed that dividing the dose may generate more confusion and lead to more medication errors. Such practice should therefore not be recommended.

Finally, when asked about how to raise awareness on medication errors, the group overall agreed that the communication on potential medication errors with methotrexate is not optimal and called for

further communication to all relevant healthcare professionals and patients/carers. It was also considered important to reinforce the communication both between healthcare professionals and between healthcare professionals and patients/carers, especially in the context of transition of care. The group recommended that communication should be clear and consistent across the EU.

Several communication tools were discussed and supported by the group such as: the circulation of a direct healthcare professional communication (DHPC), providing clear instructions on actions to be taken by healthcare professionals; a checklist for prescribers/pharmacists to facilitate discussion with patients and ensure that the prescription is clear and that critical messages are communicated to the patient; a suggestion was also made that the indication for which the medicine is prescribed should be written on the prescription in order to better inform pharmacists and other healthcare professionals involved in the dispensation/administration of methotrexate; a leaflet for patients to be given to them by the prescriber at the time of prescription (some members of the group were also very supportive of the use of new communication tools, in addition to the traditional communication tools); a patient card to be kept by the patient and shown to HCPs during transfer of care; electronic reminders / alerts within prescribing and dispensing software programs.

The group emphasised that the message should be clear, concise and consistent, and adjusted to the intended recipient, and that patients should not be overwhelmed with information. The key elements should include information on the different dosing schedules, the standard range of doses/number of tablets to be taken, and on possible confusion with folic acid.

The group also discussed visual reminders on the inner/outer packaging and agreed that it should be made clear on the packaging if the product should be 'for weekly use only'. The message should appear prominently on the pack, which should only include information relevant for HCPs and patients. There should also be an option to write on the pack the dose/number of tablets to be taken / week and on which day of the week. The addition of a calendar was not supported as it may be confusing and use too much space.

2.4. Discussion on risk minimisation measures

Root cause analysis revealed that all stages of the medication process can cause or contribute to the error. Different reasons for the occurrence of this error have been reported. However, lack of knowledge and clarity in how to use this drug was a recurring feature and not limited to patient level. Of note, admission to hospital and transfer of patients between institutions and physicians was also noted as root cause.

Taking into account the outcome of the root cause analysis and the views collected in Member States and stakeholders consultations, the PRAC discussed how the risk minimisation measures already in place could be further strengthened and if further measures should be implemented.

Visual reminders

As outcome of the PSUSA EMEA/H/C/PSUSA/00002014/201706, the marketing authorisation holders for oral methotrexate-containing products with at least one indication requiring dosing once a week were required to implement a visual reminder on the outer and immediate packaging to warn patients to take the product once a week for those indications.

The status of implementation of this measure was reviewed as part of this referral procedure as well as the corresponding mock-ups. It was noted that many different wordings and styles of warnings have been implemented, from very small information on one side of the packaging in black to large red framed information on several sides of the outer packaging, inclusion of a calendar or place to mark

the day of intake as well as different texts for the warning. In view of the differences, the PRAC recommended an increased consistency in the implementation of this measure by defining clear, concise and unambiguous warnings for the outer and inner packaging of these products (see section 3.1.2.1).

The use of a calendar on the outer packaging was supported by some stakeholders consulted in this review. However, one of the challenges in the implementation is the limited space on the packaging (e.g. for small packages or in multilingual countries), so that the text contained could only be printed in small font size. For smaller packages, the need to change carton dimensions may delay implementation. It was also considered that the use of a calendar bore the risk of confusion for the patient as some patients might believe that they have to mark every single day of the week presented. Based on all these elements, the PRAC did not agree to recommend this measure. Instead, the PRAC agreed that a place for marking a defined day of intake in full length should be foreseen in order to remind the patient or carers of the day of the week for the product to be administered. This free text field should be large enough to take into account the defined day of intake in full length to avoid any confusion.

Based on the proposals from the MAHs and after consultation of stakeholders, the PRAC was of the view that the warning on the outer package should be framed, on the front of pack, in a clearly visible place, e.g. after the information on the name and the active substance information; the letters should be of appropriate size; the respective wording and frame should be in red colour on white background, but ensuring that the warning contrasts with the rest of the packaging, the frame should include a place for the weekday of use. The indications for which the once weekly dosing applies should be referred to in grouped terms, e.g. colitis, arthritis, psoriasis, where applicable.

A shorter warning, without a reference to the day of intake, should also be implemented in a prominent place on the immediate packaging. On blisters, the warning should be repeated several times to increase the learning effect on the once weekly dosing regimen for patients.

Although the number of case reports from the EudraVigilance database was smaller than for oral formulations, it was noted that these errors had also occurred with parenteral formulations. Moreover, in a considerable number of cases, there was a lack of information on the formulation of methotrexate that had been used and therefore the exact extent of the medication error with parenteral use could not be determined. The risk of medication error by daily intake/use rather than once weekly is therefore a general problem for all methotrexate-containing products with at least one indication that requires once a week dosing. For this reason, it was considered that the visual reminder agreed for the outer packaging of the oral formulations of methotrexate should also be implemented on the outer packaging of the parenteral formulations of methotrexate with at least one indication requiring once weekly dosing, and that the shorter warning agreed for the immediate packaging of the oral formulations should be implemented on the intermediate (where applicable) and immediate packaging of the parenteral formulations. In cases where it is not technically feasible to mention it on the immediate packaging for parenteral formulations, by derogation it could be mentioned only on the intermediate packaging.

Similarly, it was considered that the same boxed warning about the dosage of methotrexate as the one agreed for all methotrexate-containing medicinal products for oral use with at least one indication requiring once weekly dosing as agreed as outcome of the PSUSA (EMA/H/C/PSUSA/00002014/201706) should be implemented in the product information of methotrexate-containing medicinal products for parenteral use with at least one indication requiring once weekly dosing (see section 3.1.2.1).

Prescribing errors

Lack of knowledge and clarity in the use of methotrexate was a recurring feature in the root-cause analysis at both patient and HCPs level. To minimise the risk of prescribing errors due to lack of knowledge of the weekly dosing schedule for methotrexate for the treatment of auto-immune diseases by the prescriber, the PRAC was of the view that methotrexate should only be prescribed by physicians with expertise in the use of methotrexate and a full understanding of the risks of methotrexate therapy. An update of the product information was recommended accordingly.

Patient groups at higher risk

The case report analyses showed that the elderly patient population was more predisposed for inadvertent daily use of methotrexate, with more than half of the cases reporting elderly population (65 or over). Other subgroups of patients were also identified at risk such as patients with impaired memory and cognitive functions, patients with visual impairment, patients who have difficulties to follow written instructions, patients with co-morbidities and co-medications. These discussions reflect the risk factors that have also been identified as root causes and may apply to elderly, as well as adult patients.

As understanding of once a week intake of oral methotrexate is essential to avoid dosing errors by the patients or their carer and for the adherence to this special treatment schedule, an update of the product information was considered necessary to alert healthcare professionals to restrict the use of oral methotrexate to patients/carers who are able to comply with the once weekly dosing schedule.

Division of the dose in several intakes

Cases of medication error have been reported where the prescribed dose was divided in several intakes such as 3 doses taken every 12 hours. Such treatment regimen is recommended in the product information of some products. Requested to justify such recommendation to split the dose, the MAHs referenced published literature of variable quality with some of the studies having significant limitations. One study, which was cited by several MAHs in support of dividing the dose, had imbalances in disease severity between treatment groups at baseline, which could have affected the study outcome (Dhaon et al., 2018 [10]). Pharmacokinetic studies in patients with rheumatoid arthritis have demonstrated improved bioavailability when splitting a single oral methotrexate dose of 25-35 mg/week into two doses, given with an 8- hour interval (Hoekstra et al., 2006 [15]) and systemic exposure of oral methotrexate was shown to plateau at doses ≥ 15 mg/week (Schiff et al., 2014 [24]). A recent systematic literature review also referred to improved GI absorption when doses above 15 mg are split into two doses, given ≥ 8 hours apart (Goodman et al., 2015[13]). However, the effectiveness of this regimen is not supported by adequate data. No randomised controlled clinical trials with appropriate sample sizes, which would conclusively answer the question, if splitting of oral methotrexate doses has advantages for patients, are missing. It was also noted that current European guidelines do not mention the possibility of dividing the dose.

Stakeholders consulted on the clinical evidence / experience to support alternative dosing schedules and dose splitting were not aware of any robust supportive evidence for such a recommendation and could not identify a patient group for whom benefits of dividing the dose would outweigh the risk of medication errors. It was also highlighted that alternative measures such as switching from an oral to a subcutaneous formulation, increasing the dose of folic acid or use of ondansetron could be considered to mitigate the risk of gastrointestinal adverse events. Overall, it was agreed that dividing the dose may generate more confusion and lead to more medication errors. Such practice therefore should not be recommended and the PRAC recommended the update of product information to remove such regimen if described.

Educational material and communication

From the consultation of stakeholders, it emerged that further communication to all relevant healthcare professionals and patients/carers are necessary, in particular to reinforce the communication between healthcare professionals and between healthcare professionals and patients/carers, especially in the context of transition of care. It was recommended that communication should be clear and consistent across the EU.

To increase the awareness of HCPs and patients on the risk of medication errors and their possible consequences, the PRAC was of the view that educational materials for healthcare professionals were necessary, in particular for the oral formulations of methotrexate with at least one indication requiring a once weekly dosing. Parenteral formulations are used in more specific cases where healthcare professionals are more likely to supervise the administration methotrexate, which decreases the risk of medication errors. For these formulations, visual reminders on the outer and inner packaging as well as the added wording in the product information is considered to be sufficient to remind healthcare professionals and patients about the weekly dosing schedule.

The educational material for healthcare professionals should in particular provide information on the potential for fatal overdose due to medication errors, including daily instead of once weekly use, highlight the need to inform patients and relatives/carers about the once weekly dosing, and provide information on the importance to fill in prescriptions with clear instructions about once weekly dosing, defined day of intake, and to not use abbreviations. The educational material should also include a reminder for the pharmacist to counsel the patient about the inadvertent daily instead of once-weekly dosing.

Since various educational materials are already in place in some Member States, and to avoid duplication, the PRAC considered that in case education materials would already be available, these should be updated to reflect the key elements agreed. In the absence of any education material for HCPs, those should be developed, preferably in the form of a checklist.

In addition, the PRAC requested the development of a patient card to be inserted in or attached to the outer packaging. This card should remind patients of the weekly dosing schedule of their methotrexate treatment, to write the day of the week for intake on the card, to inform them about the serious adverse effects that may be fatal and on the symptoms of overdose and steps to be taken should symptoms arise, and recommend patients to always show the card and alert any healthcare professionals not familiar with their methotrexate treatment about their once weekly dosing schedule (e.g. on hospital admission, change of care).

Use of large packaging

The root cause analysis has shown that large packaging was a source of errors and may increase the risk of overdose. In particular, it was reported that bottle/tube packaging for tablet formulations does not allow adequate tracking, i.e. easy counting, of the remaining tablets, making it difficult both for patients and caregivers to notice the error. To keep track, the content of the entire bottle would need to be emptied to check for the remaining tablets while handling a cytotoxic substance. It was also raised that rheumatic patients using bottle packaging with child-resistant-caps might have issues in opening the bottles and remove all the tablets from the new bottle packaging into an older one where the child-resistant cap has become worn off. In addition, tablets available in bulk packaging are commonly repacked, in particular in medical centres and hospitals, potentially resulting in loss of warning information.

To minimise any risk associated with the use of bulk packaging, it is considered that bottles and tubes as inner packaging for tablet formulations of methotrexate should be replaced by blisters as it would allow a protection for each tablet and mentioning of adequate warnings.

This measure was discussed as an important risk minimisation measures by the stakeholders consulted in the context of this procedure and was supported by both HCPs and patient representatives.

Concerns were expressed about child-proofing of blister packs and use by patients with rheumatoid arthritis. To ensure that the blisters' design meets patients' needs and takes into account any physical disabilities, the blisters should be designed according to the target population that will use it and be 'user tested'.

Taking into account that such replacement may require several technical changes and not to jeopardize the availability of methotrexate formulations in some Member States, the PRAC agreed on an implementation period of up to 4 years. It was noted that a number of MAHs have already initiated the replacement of bottles by blisters. The MAHs will need to report on the progress of implementation of this measure in future PSURs.

In addition, in view of the risk of daily instead of weekly administration associated with large pack sizes of methotrexate-containing medicinal products, reducing the number of tablets per package for the indications requiring once weekly dosing was considered by most stakeholders consulted as an essential measure to underline the weekly dosing scheme and ensure that no repackaging is necessary. Supportive arguments for reducing the package size included increased patient's awareness by smaller packages and earlier detection of the error, if daily dosing occurs. An additional burden on patients was recognised, but considered acceptable, if it would lead to a reduction in the risk of this medication error, which may be fatal. In view of the variety of strengths available and the required doses (e.g. titration needed) no clear proposal on the optimal pack size could, however, be agreed upon and thus, no restrictions on the pack size were recommended by the PRAC.

Separation of presentations

Confusion due to methotrexate products being authorised for different indications with different dosing schedule is considered as an important risk factor for medication error. A separation of presentations for use in autoimmune diseases requiring a once weekly dosing from the presentations for use in oncologic indications was considered useful to minimise the risk of medication errors and strongly supported by stakeholders consulted in the context of this procedure. Recognised advantages are the possibility of specific warnings on the package for the used indication if presentations are separated, as well as minimisation of the risk for dosing errors in cases where methotrexate products are self-administered by patients. In addition, it was considered useful if the two presentations would have different names, to clearly distinguish presentations intended for weekly use, e.g. by adding a qualifier to emphasise the weekly dosing schedule of administration.

Whilst it would imply the registration of new marketing authorisation and a variation of the existing ones, the MAHs are strongly encouraged to separate oncologic and autoimmune diseases indications and market two different medicines, with different names, different packaging, different package leaflets etc. A specific and well-designed packaging for use in autoimmune diseases aiming at avoiding the risk of confusion and help patients to take the proper dose of methotrexate weekly should be developed (different outer appearances).

Limiting the availability of tablets to the 2.5mg strength

In the context of this procedure, it was discussed that limiting the availability of tablets to the 2.5mg strength could help to minimise the risk of severe adverse reactions, should daily instead of weekly medication errors occur. Although the range of available strengths is already restricted in a number of

Member States, concerns were raised that the limitation of availability of tablets to the 2.5 mg strength may lead to further medication errors, whereby patients lose track of the number of tablets taken, which in turn may lead to overdose or underdose, especially when higher doses are prescribed and in the case of poly-medicated patients. Concerns were also raised that the need to take a higher number of tablets may give the impression that the drug has to be taken daily and that patients with impaired dexterity may be tempted to take tablets daily in order to decrease the number of tablets having to be released per day. Differences in local market legislation between different countries were also considered to pose a challenge for the suggested limitation of the availability of different strengths.

Another concern was that reducing the availability of tablets strengths to 2.5 mg for methotrexate-containing products may not be suitable for use in oncology indications in view of the higher doses of methotrexate to be used (from 20 - 40 mg/m²); indeed, a large number of tablets per dose would be needed to cover these dose ranges if only 2.5 mg tablets were available. In addition, it was noted that lactose is one of the main excipients of the tablets and taking too many tablets may increase the risk of diarrhoea. In view of the above, no restrictions on the availability to certain strengths were recommended by PRAC.

Confusion with folic acid tablets

Taking into account the reported cases of medication errors due to mix-up of dose schedules between methotrexate and concomitant treatment with daily dosing schedule such as folic acid, MAHs should further increase difference in appearance between folic acid tablets and methotrexate-containing tablets (e.g. colour, size). Further discrimination between the outer packaging should also be considered.

Electronic prescribing and dispensing software programs and other electronic applications

As highlighted by the root cause analysis presented above, some dosing errors have been reported due to inadequacy of electronic prescribing and dispensing software programs to highlight prescribers and pharmacists of the weekly dosing schedule of methotrexate for the treatment of auto-immune diseases. An update of the electronic prescribing and dispensing software systems for hospitals, physician offices and pharmacies with regard to methotrexate once weekly prescriptions should be envisaged. The following aspects may be considered: default weekly (rather than daily) dosing schedule for oral methotrexate orders; a hard stop verification and mandatory entry of an appropriate oncologic indication when the clinician selects a daily schedule for oral methotrexate orders; lock down frequency "once weekly" of dose set as default or setting that cannot be overridden; user to be prompted to record clinical evidence to support this change; once-weekly methotrexate prescriptions with a specified dose range (e.g. a maximum of 25-30 mg); "High alert drug" pop up when methotrexate is prescribed. In hospital systems and electronic medication administration records (eMARs), it is suggested to link methotrexate order entry and verification to laboratory results (e.g. CBC, serum creatinine, liver enzymes) to prompt review of the renal function and other monitoring parameters by prescribers, pharmacists, and nurses.

PRAC recommended national competent authorities to take due account of the above proposals. National competent authorities may also consider further evaluating approaches such as smartphone application to increase patients' awareness on the weekly dosing schedule of methotrexate when indicated in auto-immune diseases, with receipt of notification on the planned day of intake.

Management plan for hospitals

A number of medication errors were reported following errors of prescription/dispensing/administration at the hospital. The PRAC identified a number of key elements listed below, which may be considered for general management of methotrexate, at time of patient admission and for management on wards.

General management: low dose methotrexate for once weekly use should be classified as “High alert/risk medicine”, labelled as such by the pharmacy and administered in a risk-sensitive manner to the patient; regular training to the medical staff on the handling of high-risk drugs, in particular low dose methotrexate with once weekly dosage should be ensured, according to the internal regulations in the individual clinics; compliance with inpatient (and outpatient) management should be audited; an error reporting system should be established; a “pharmacist on ward” may be considered as a general measure to prevent medication errors; the hospital pharmacist should daily check all methotrexate prescriptions; the prescription and administration software systems used in the hospital should be checked by a responsible person (e.g. hospital pharmacist).

Admission management: methotrexate should be automatically stopped on admission, no self-administration should be permitted; all transcriptions with regard to methotrexate should be double-checked; baseline blood examination and anamnesis of medicinal products taken (medication reconciliation) should be documented and signed by a named responsible person; hospital pharmacist should perform medicines reconciliation on admission and in case of any new prescriptions: confirmation of once weekly dose (strengths and number of tablets), check of indication, defined weekday of intake, contraindications and interactions, check patient’s own drugs, check that methotrexate is highlighted in the electronic system, make entry in progress notes stating “pharmacist admission review completed”; methotrexate should only be prescribed and dispensed on an individual basis in a pre-specified process (e.g. special prescriptions, a special process in electronic system) and in unit doses; prescription of methotrexate should be co-signed by a named specialist experienced in the use of methotrexate; medication should be double-checked before administration (e.g. nurse/nurse or nurse and doctor; bedside scanning, if available); details of the weekly dose, weekday of intake and strength and number of tablets should be included in the patient record and highlighted.

Management on wards: the hospital pharmacist should only deliver the number of doses needed for the individual patient; unit doses with information on content, data of the patient, dose and information “only once weekly” as well as the day and date of application should be marked; a visible warning should be fixed on the unit dose pack (e.g. label, icon: “risk medicine”); remaining doses of methotrexate should be returned to the pharmacy; a list of high-risk drugs should be available on ward; methotrexate once weekly should be included and the once weekly dosing regimen highlighted.

Discharge management: physicians/pharmacists should ensure that patients who are to be discharged from hospital and for whom methotrexate is prescribed receive adequate counselling. For these patients, all discharges should be reviewed and signed by a pharmacist and/or a second named specialist.

Information to the general practitioner who will continue to supervise and monitor therapy with methotrexate should include the following: indication, dose, information on application interval (e.g. once weekly), day of the week for application (in full, no abbreviations should be used), laboratory control values, reference to regular check-ups.

Information for the patient should include verbal and written instructions (e.g. medication plan) that specify the weekly dosing schedule and emphasize the danger of taking extra doses. Patients should repeat back the instructions to validate understanding of the weekly dosing schedule and the toxicities if taken more frequently than prescribed. A medication plan including dose, application interval (once weekly), day of the week for application, information that errors may result in serious adverse and sometimes fatal reactions should be given to the patient. The patient should be informed about early signs and symptoms of overdose and, when it occurs, the doctor should be consulted immediately.

The PRAC recommends the Member States to take due account of the above proposals.

3. Risk management

The Committee, having considered all information and data submitted in the procedure, recommends a series of pharmacovigilance activities and risk minimisation measures to further characterise and minimise the risk of medication errors associated with methotrexate.

3.1. Risk management plan

The risk of medication errors due to inadvertent daily instead of once weekly dosing should be considered an important identified risk in the risk management plan.

Each MAH of methotrexate-containing products for which additional risk minimisation measures have been recommended, i.e. all oral formulations of methotrexate with at least one indication requiring once weekly dosing, should operate a risk management system to be described in an RMP. The RMP should include and reflect all the pharmacovigilance activities and risk minimisation measures listed below.

3.1.1. Pharmacovigilance activities

3.1.1.1. Targeted follow-up questionnaires

The PRAC considered that targeted follow-up questionnaires should be implemented for all reported cases of medication errors with methotrexate resulting in overdose in the EU. The content of this questionnaire was agreed by PRAC. This targeted follow-up questionnaire should be reflected in the RMP as a routine pharmacovigilance activity.

3.1.1.2. Measurement of the effectiveness of the risk minimisation measures

To ensure consistency a case analysis in the EudraVigilance database using the same search terms and criteria as used for this procedure (see table below) will be performed in the context of future PSUSA assessments.

| EVDAS-Prompts | |
|------------------------------------|--|
| Active Substance (High Level) | Methotrexate |
| MedDRA Reaction Terms | SMQ Medication Errors (Broad) |
| EV Document Type | EVPM |
| Report Type | Spontaneous, Other, Not available to sender (unknown), Report from Studies |
| Medicinal Product Characterisation | Suspect, Interacting, Drug not Administered |
| Origin | EEA |
| Receive Date | To be confirmed |

Enhanced case line listings for the SMQ (broad) in the EEA will be further analysed to identify cases of inadvertent daily instead of weekly usage. In addition to information provided directly in the EudraVigilance database (e.g. EV safety report identifier, case report number, report type, country, receive date, age, sex, primary source qualification, serious, seriousness death, seriousness

hospitalization, literature reference, recoded drug list, suspect/interacting enhanced reported drug list, concomitant/not administered enhanced reported drug list, indication PT of the drug of interest as reported in the ICSR, reaction list PT), specific information will be extracted from the ICSRs and case narratives such as formulation (oral, parenteral, unknown), length of treatment prior to the error (=duration), time drug was used between error and event (in days) (= Time to Onset), daily dose (mg), cumulative dose between error and event, and root cause.

Cases of medication errors that do not result in an adverse drug reaction and which are not reported to EudraVigilance (medication errors without harm, intercepted medication errors and potential medication errors) should be further substantiated by the MAHs by using the follow-up questionnaire and should be reported by the MAHs through the PSURs.

Taking into account the PRAC criteria for impact research, as well as the very high number of products and MAHs concerned, and in order to obtain meaningful and reliable results regarding the effectiveness of the risk minimisation measures recommended, the PRAC also considers that the regulatory actions proposed for methotrexate-containing medicinal products would benefit from the conduct of an independent EMA-funded study in accordance with the principles laid down in the PRAC Strategy on Measuring the Impact of Pharmacovigilance Activities (Rev 1) ([EMA/165407/2017](#)).

3.1.2. Risk minimisation measures

3.1.2.1. Routine risk minimisation activities

Amendments to the product information

The PRAC considered that routine risk minimisation measures in the form of updates to the product information would be necessary in order to minimise the risk of medication errors associated with the use of methotrexate-containing medicinal products with at least one indication requiring once weekly dosing.

These changes include amendments to section 4.2 of the SmPC to reflect the information that only physicians with expertise in using methotrexate and full understanding of the risks of methotrexate therapy should prescribe these products. For oral formulations, section 4.2 of the SmPC should also include the requirement that healthcare professionals should ensure that patients or their carers will be able to comply with the once weekly regimen. Changes also included the deletion of any recommendations to split the dose from the SmPC. The package leaflet should be amended accordingly.

In addition, section 4.2 of the SmPC and section 3 of the packaging leaflet of methotrexate-containing medicinal products for parenteral use with at least one indication requiring once weekly dosing should be amended to include the same warning on the dosing schedule of methotrexate in relevant indications as the one already agreed for methotrexate-containing medicinal products for oral use with at least one indication requiring once weekly dosing (as agreed as outcome of the PSUSA - EMEA/H/C/PSUSA/00002014/201706).

The PRAC also recommended labelling changes for methotrexate-containing medicinal products with at least one indication requiring once weekly dosing to include visual reminders that the product should only be taken once a week, on the outer and immediate packaging for oral formulations and on the outer, intermediate and immediate packaging for parenteral formulations. In case where it is not technically feasible to mention it on the immediate packaging for parenteral formulations, by derogation it could be mentioned only on the intermediate packaging.

On the outer packaging, the visual reminder should be framed, on the front of the pack, in a clearly visible place, e.g. after the information on the name and the active substance information; the letters should be of appropriate size to be easily readable; the respective wording and frame should be in red colour on white background, but ensuring that the warning contrasts with the rest of the packaging, the frame should include a place for the weekday of use.

On the intermediate and/or immediate packaging, a shorter warning, without a reference to the day of intake, should also be implemented. On blisters the wording should be printed repeatedly in one or more (e.g. on multilingual packages) rows depending on readability. On other immediate packaging it should be implemented once only in a prominent place.

The indications for which the once weekly dosing applies should be referred to in grouped terms, e.g. colitis, arthritis, psoriasis, where applicable, to keep the wording concise.

In addition, the labelling of methotrexate-containing medicinal products for oral use with at least one indication requiring once weekly dosing was also amended to include the agreed wording for a patient card (see below).

3.1.2.2. Additional risk minimisation activities

Packaging

For tablet formulations of methotrexate containing products for oral use, the PRAC recommended that bottles or tubes used as immediate packaging should be replaced by blisters within 4 years after finalisation of this referral procedure. This implementation period was considered necessary to take into account the several technical changes such replacement may require and not to jeopardize the availability of methotrexate formulations in some Member States.

This measure should be listed as a risk minimisation measure in the risk management plan and a progress report should be provided in future PSURs. This report should provide precise and clear status in all Member States for the replacement of the bottles and tubes by blisters in all EU member states where they are currently authorised. MAHs should notify forthwith the relevant NCAs of any feasibility issue that would delay the implementation of this measure.

Educational materials

Educational measures are necessary in order to increase the awareness of HCPs and patients on the risk of medication errors with methotrexate for oral use when used in indications requiring a once weekly dosing and their possible consequences.

- Educational material(s) for healthcare professionals

The PRAC requested the development or the amendment of any existing educational material for healthcare professionals. This educational material shall contain the following key elements:

- The potential for fatal overdose due to medication errors (ME), including daily instead of once weekly use;
- The need to inform patients and relatives/carers about the once weekly dosing;
- Information on the importance to fill in prescriptions with clear instructions about once weekly dosing, defined day of intake, and to not use abbreviations;
- The pharmacist should counsel the patient about the inadvertent daily instead of once-weekly dosing.

The educational material for healthcare professional should be read in conjunction with the summary of product characteristics.

The format of the educational material(s) is left at the discretion of the NCAs in order to select the most suitable format in the relevant territory taking into consideration the existing material(s) and the characteristics of the national healthcare system. The final version must be agreed with the National competent authorities in each Member State.

- Patient Card

The PRAC also requested the development of a patient card to be inserted inside or attached to the outer packaging depending on the feasibility. PRAC agreed on a wording which will remind patients to take the product only once weekly and write the day of the week for intake on the card, inform on serious adverse effects that may be fatal, on the symptoms of overdose and steps to be taken should symptoms arise, and recommend patients to show the card and alert any healthcare professionals not familiar with their methotrexate treatment about their once weekly dosing schedule (e.g. on hospital admission, change of care). The agreed wording is to be reflected in the product information of methotrexate-containing products for oral use with at least one indication requiring weekly dosing.

3.1.2.3. Direct Healthcare Professional Communication and Communication plan

The PRAC considered that a direct healthcare professional communication (DHPC) was needed to raise awareness of the new recommendations and other risk minimisation measures agreed.

This communication should be distributed to all healthcare professionals involved in prescribing, dispensing and handling of methotrexate-containing products (e.g. physicians and pharmacists). Target groups should be further defined at national level, depending on national health care systems.

All concerned MAHs in each Member State are encouraged to liaise with national competent authorities to collaborate in order to prepare and circulate a single DHPC in each Member State.

4. Recommendations and conclusions on benefit-risk

The risks associated with inappropriate use of methotrexate daily instead of weekly make methotrexate one of the most known high-risk medications prone to medication errors. Systematic review by Saedder and colleagues (2014) [21] revealed that 47% of all serious medication errors were caused by only seven drug classes, with methotrexate topping the list in percentage of incidents. Furthermore, of the 74 articles that met the review's inclusion criteria, 73 contained information about a serious adverse reaction caused by methotrexate-related medication error (found in the FDA Adverse Event Reporting System). Since early 1996, harmful or fatal errors with low dose oral methotrexate have been reported to the Institute for Safe Medication Practices (ISMP) and published in more than 50 of its newsletters, but in spite of this and numerous risk minimization measures, methotrexate continues to be subject in documented serious medication errors (Grissinger, 2018 [14]).

In EU/EEA, despite the risk minimisation measures in place, cases of medication errors are still occurring. In order to assess the root causes and the impact of the risk of medication errors due to inadvertent daily dosing instead of weekly dosing, the PRAC considered the analyses of cases report of inadvertent daily instead of weekly usage of methotrexate-containing products, including reports without adverse events, for the period 1 January 2013 until 31 March 2018 from the EudraVigilance database as well as from the data provided by the MAHs of methotrexate-containing products which included analyses of the medication error case reports from the companies' pharmacovigilance databases and in the literature. The data showed that severe, life-threatening and fatal cases of overdose due to medication errors with methotrexate-containing medicinal products continue to be

reported despite the risk minimisation measures in place. While daily instead of once weekly use of methotrexate was mainly reported with oral dosage forms in non-oncologic indications, predominantly rheumatoid arthritis and psoriasis, there were also cases with the use of parenteral formulations, as well as many reports which did not specify the route of administration.

Extensive assessment of spontaneously reported post-marketing cases has been performed by the PRAC and although some relevant data might not have been provided in all spontaneously reported post-marketing cases, the root cause analysis was further substantiated by the assessment of literature data, which provided more detailed description of methotrexate medication error cases. The feedback received from healthcare professional organisations also provided further insight on the root causes for errors.

Based on the available data, the PRAC noted that the abovementioned risk of medication errors can occur at all stages of the medication process, from prescription to administration. Different reasons for the occurrence of medication error have been identified. The ambiguity due to the product being authorised in different indications with different dosing schedules and lacking clear and visible warnings alerting on the once weekly dosing schedule on the packaging and the use of bulk packaging were identified as root causes for medication errors. Lack of knowledge and clarity on the weekly dosing schedule in some indications was also recurring feature and not limited to patient level. Admission to hospital and transfer of care between institutions and physicians was also noted as a root cause due to poor or a lack of communication between patient/physician, physician/physician, physician/nurse. Dispensing errors have also been reported. The case report analyses showed that the elderly patient population was more predisposed for inadvertent daily use of methotrexate, with more than half of the cases reporting elderly population (65 or over). Other subgroups of patients were also identified at risk such as patients with impaired memory and cognitive functions, patients with visual impairment, patients who have difficulties to follow written instructions, patients who split their weekly oral methotrexate dose, patients with co-morbidities and co-medications.

In the context of this review, the PRAC discussed, in consultation with patients and healthcare professionals, how the risk minimisation measures already in place could be further strengthened and if further measures should be implemented.

To increase awareness and remind healthcare professionals and patients of the weekly dosing schedule required for the treatment of some conditions, the MAHs for oral methotrexate-containing products with at least an indication requiring dosing once a week had been requested, as outcome of the PSUSA (EMA/H/C/PSUSA/00002014/201706), to implement a visual reminder on the outer and immediate packaging to warn patients to take the product once a week for those indications requiring dosing once a week. It was noted that many different wordings and styles of warnings have been implemented, from very small information on one side of the packaging in black to large red framed information on several sides of the outer packaging, inclusion of a calendar or place to mark the day of intake as well as different texts for the warning. In view of the differences, the PRAC recommended an increased consistency in the implementation of this measure by defining clear, concise and unambiguous warnings for the outer and inner packaging of these products. In addition, although the number of cases reporting medication errors with parenteral formulations was smaller than with oral formulations, the risk of medication error by daily intake/use rather than once weekly is considered a general problem for all methotrexate-containing products with at least one indication that requires once a week dosing. For this reason, the PRAC was of the view that the visual reminder agreed for the outer packaging of the oral formulations of methotrexate should also be implemented on the outer packaging of the parenteral formulations of methotrexate with at least one indication requiring once weekly dosing, and that the shorter warning agreed for the immediate packaging of the oral formulations should be implemented on the intermediate (where applicable) and immediate packaging of the parenteral formulations. Similarly, the boxed warning in SmPC section 4.2 already agreed to be added

to the product information of the oral formulations as outcome of the PSUSA should be also reflected in the product information of methotrexate parenteral formulations.

Medication errors were also associated with the use of bulk packaging. In particular, it was reported that bulk packaging such as bottles or tubes does not allow tracking, i.e. easy counting, of the remaining tablets, making it difficult both for patients and caregivers to notice the error. In addition, bulk packaging bear the risk of losing warning information at the time of repackaging which is e.g. common practice in medical centres/hospitals. To address this issue, the PRAC recommended that for all tablet formulations of methotrexate, bulk packaging such as bottles or tubes should be replaced by blisters. Taking into account that such replacement may require several technical changes and not to jeopardize the availability of methotrexate formulations in some Member States, the PRAC agreed to an implementation period of up to 4 years after finalisation of this procedure.

To minimise the risk of prescribing errors due to lack of knowledge by the prescriber of the weekly dosing schedule of methotrexate for the treatment of auto-immune diseases, the PRAC was of the view that methotrexate should only be prescribed by physicians with expertise in the use of methotrexate and a full understanding of the risks of methotrexate therapy. An update of the product information of all methotrexate products with at least one indication requiring a once weekly dosing schedule was recommended accordingly. In addition, as understanding of the once weekly dosing schedule of methotrexate is essential to avoid dosing errors by the patients or their carer and for the adherence to this special treatment schedule, an update of the product information of methotrexate products with at least one indication requiring a once weekly dosing schedule was considered necessary to alert healthcare professionals to restrict the use of oral methotrexate to patients/carers who are able to comply with the once weekly dosing schedule.

Dividing the prescribed dose in multiple intakes was reported as a risk factor for medication error and no robust evidence could be provided to support the effectiveness of this regimen or identify patient groups for whom benefits of dividing the dose would outweigh the risk of medication errors. It was also noted that current European guidelines do not mention the possibility of dividing the dose. Overall, it was considered that such practice may generate more confusion and lead to more medication errors and should therefore not be recommended. Any reference to dividing the dose in the product information should therefore be deleted.

To increase awareness of HCPs on the risk of medication errors and their possible consequences, it was considered that for methotrexate oral formulations, educational materials for healthcare professionals should be developed or updated, if already in place, to inform them on the potential for fatal overdose due to medication errors (ME), including daily instead of once weekly use, highlight the need to inform patients and relatives/carers about the once weekly dosing, and provide information on the importance to fill in prescriptions with clear instructions about once weekly dosing, defined day of intake, and to not use abbreviations. The educational material should also include a reminder for the pharmacist to counsel the patient about the inadvertent daily instead of once-weekly dosing.

In addition, the PRAC requested the development of a patient card to be inserted inside or attached to the outer packaging. This card was considered a necessary tool to remind patients to take the product only once weekly, inform on serious adverse effects that may be fatal, on the symptoms of overdose and steps to be taken should symptoms arise, and recommend patients to show the card and alert any healthcare professionals not familiar with their methotrexate treatment about their once weekly dosing schedule (e.g. on hospital admission, change of care). The day of the week methotrexate treatment should be taken should be written on the card by the patient.

The risk of medication errors due to inadvertent daily instead of once weekly dosing is an important identified risk and all methotrexate-containing products for which additional risk minimisation measures are required to address this risk (i.e. replacement of bottles/tubes by blisters,

6. Grounds for recommendation

Whereas,

- The Pharmacovigilance Risk Assessment Committee (PRAC) considered the procedure under Article 31 of Directive 2001/83/EC for medicinal products containing methotrexate;
- The PRAC considered the totality of the data submitted for methotrexate containing products with regard to the important identified risk of medication errors when methotrexate intended for once weekly use is taken daily by mistake, the root causes for this risk and the effectiveness of the risk minimisation measures in place. This included the responses submitted by the marketing authorisation holders in writing as well as the views of patients and healthcare professionals;
- The PRAC investigated the root causes for the abovementioned risk of medication errors and noted that these can occur at all stages of the medication process;
- The PRAC noted that severe, life-threatening and fatal cases of overdose due to medication errors with methotrexate-containing medicinal products continue to be reported and that the risk minimisation measures in place have not been sufficiently effective to prevent medication errors, in particular with the oral formulations of methotrexate;
- The PRAC concluded that there is a need to further strengthen the current risk minimisation measures by adding warnings in the product information and visual reminders on the outer, intermediate and immediate packaging of methotrexate-containing medicinal products with at least one indication requiring a once weekly dosing, for both oral and parenteral use;
- In addition, the PRAC also recommended other changes to the product information of all methotrexate-containing products with at least one indication requiring once weekly dosing to include that only physicians with expertise in using methotrexate-containing medicines should prescribe them and that healthcare professionals should ensure that patients or their carers will be able to follow the once weekly dosing schedule. In addition, splitting the dose in multiple intakes should no longer be recommended;
- Considering the number of reported inadvertent daily administration of methotrexate oral formulations, the PRAC concluded that for these products, educational materials for healthcare professionals should be developed or updated, if already in place, in accordance with the key elements agreed, as well as a patient card to be provided with the medicinal product, to further increase awareness. It was also agreed that for all tablet formulations of methotrexate, bottles and tubes currently used as immediate packaging should be replaced by blisters. These risk minimisation measures should be reflected in a risk management plan.
- A direct healthcare professionals communication was also agreed, together with a communication plan;
- The PRAC finally agreed on targeted follow-up questionnaires should be used for all cases of medication errors reported with methotrexate and resulting in overdose.

In view of the above, the Committee considers that the benefit-risk balance of methotrexate-containing medicinal products remains favourable subject to the agreed conditions to the marketing authorisations, and taking into account the agreed amendments to the product information and other risk minimisation measures.

The Committee, as a consequence, recommends the variation to the terms of the marketing authorisations for methotrexate-containing medicinal products.

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