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Safety Analysis Insight: Medication errors reported with methotrexate

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A medication error is an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient. Mistakes in the prescribing, dispensing, storing, preparation and administration of a medicine are the most common preventable cause of undesired adverse events in medication practice and present a major public health burden (European Medicines Agency, 2022). 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 revealed that 47% of all serious medication errors were caused by only seven drug classes, with methotrexate topping the list in percentage of incidents (Saedder EA, 2014).

Methotrexate is indicated in the treatment of cancers such as acute lymphoblastic leukaemia and various inflammatory conditions, including rheumatoid arthritis, juvenile idiopathic arthritis, psoriasis, and psoriatic arthritis and as steroid sparing adjunctive therapy in Crohn's disease.

Methotrexate toxicity is characterized by nausea, vomiting, diarrhea, myelosuppression, pancytopenia, liver dysfunction, acute renal failure, pulmonary symptoms, mucositis, stomatitis, ulceration/erosion of the gastrointestinal system and cutaneous ulcerations (Tan KW, 2011) (Jakubovic BD, 2013) (Shiver MB, 2014). 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.

On 22 March 2018 Spain triggered a referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data, and requested Pharmacovigilance Risk Assessment Committee (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.

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.

In conclusion, the following conditions to the marketing authorisations and other actions were requested:

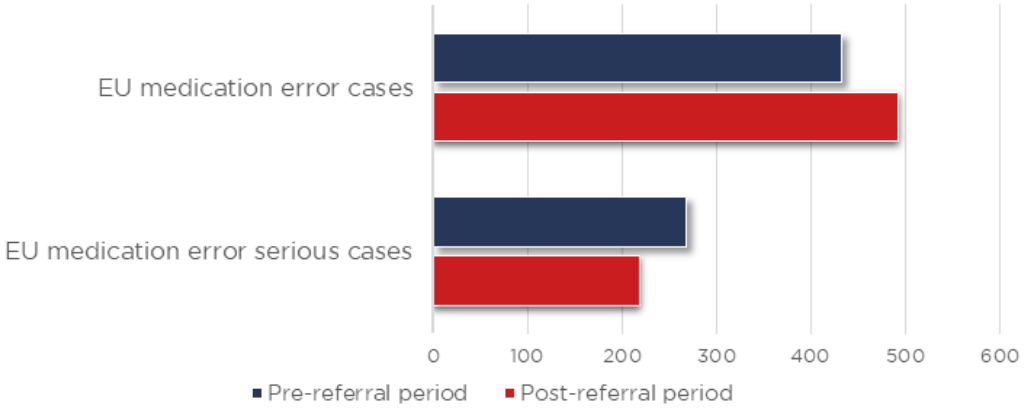
Action	Timeline
Conditions to the marketing authorisation	
All methotrexate-containing products Each MAH should implement the agreed targeted follow-up questionnaires for all medication errors resulting in overdose.	From the date of notification of the Commission Decision
Methotrexate-containing products for oral use with at least one indication requiring once weekly dosing Each MAH should operate a risk management system to be described in a risk management plan (RMP) which shall be submitted to the relevant Competent Authorities. The RMP should reflect the following additional risk minimisation measures to address the important identified risk of medication errors resulting in overdose: - educational material(s) for healthcare professionals developed in accordance with the key elements agreed; - the agreed patient card. For tablet formulations, the following measure should also be implemented: MAHs should replace any bottle or tube used as immediate packaging by blisters.	Within 3 months after Commission decision Within 4 years after Commission decision
Other risk minimisation measures	
Consistent 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.	
Boxed warning in SmPC section 4.2 should be also reflected in the product information of methotrexate parenteral formulations.	
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.	
A direct healthcare professionals communication (DHPC) was also agreed, together with a communication plan	

In view of the left, the PRAC considered that the benefit-risk balance of methotrexate-containing medicinal products remained 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 (PRAC aAssessment report, 2019). In EU/EEA, despite the risk minimisation measures in place, cases of medication errors are still occurring. The aim of this article was to compare reporting trends of medication errors reported with metho-trexate in EU for pre- and post-referral period.

A review of cases of medication errors reported with methotrexate from the available safety data was performed for comparable intervals in the pre-referral (01-Sep-2016 – 31-Mar-2018) and post-referral period (01-Sep-2020 – 31-Mar-2022). Post-referral period was determined taking into account that some time was required for implementation of risk minimisation measures, for e.g. for national approvals of educational materials and DHPC. A detailed quantitative assessment could not be performed due to limited information available in the case reports, lack of information on the exposure and other known limitations of spontaneous reporting. Therefore, reporting trends of medication errors related to methotrexate use in EU were compared for pre- and post-referral period. The number of cases from the rest of the world for the same intervals was also reviewed. Cases were retrieved with the MedDRA SMQ Medication Errors (broad), while additional analysis was performed for cases with PT of Overdose, considering the fact that once daily instead of once weekly dosing of methotrexate leading to drug overdose is the most concerning medication error.

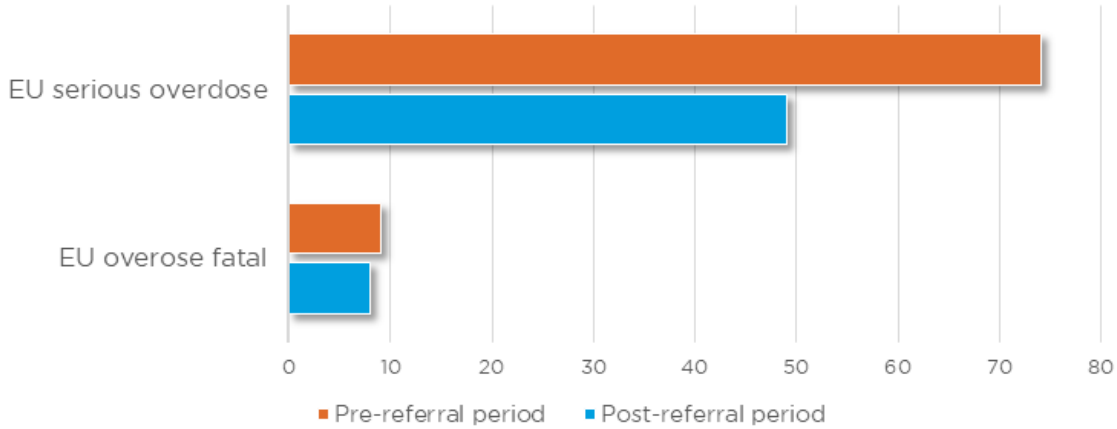
Although the total number of medication error cases reported from EU was higher after the referral, the number of serious cases was lower, as presented on Figure 1.

Figure 1: Number of medication error cases reported with methotrexate from EU, for pre-referral and post-referral periods



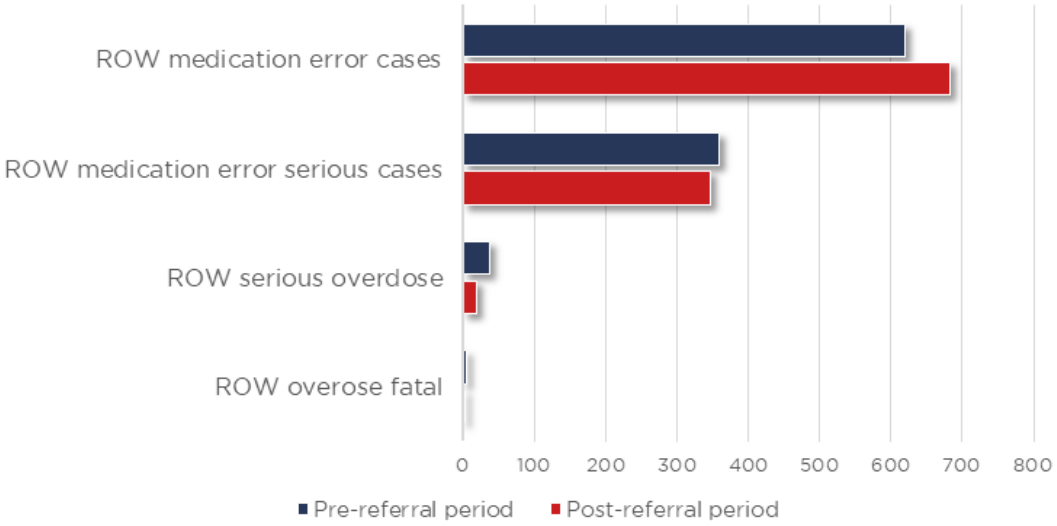
Number of serious overdose cases from EU, including cases which resulted in fatal outcome, also decreased, as presented on Figure 2.

Figure 2: Number of serious overdose cases reported with methotrexate from EU, for pre-referral and post-referral periods



Similar trends were noted for the rest of the world (African Region, Eastern Mediterranean Region, Region of the Americas, South-East Asia Region, Western Pacific Region), which is presented on Figure 3.

Figure 3: Number of medication error cases reported with methotrexate from the rest of the world, for pre-referral and post-referral periods



In conclusion, reporting rates of serious cases of medication errors reported with methotrexate in EU, including cases of overdose, decreased in the period post-referral, when compared to pre-referral period. Further research is needed to quantify the impact of introduced risk minimisation measures. Considering methotrexate's high potential for medication errors, it is essential to appropriately educate healthcare professionals, care-givers and patients about it's appropriate use. Although it is sometimes challenging to assess their effectiveness, introduced risk minimisation measures, together with routine measures, are very important for ensuring patients' safety. A variety of tools are currently available for additional risk minimisation. This field is continuously developing, and new tools are likely to be developed in the future (GVP Module XVI).

References

EMA. (2017). Guideline on good pharmacovigilance practices (GVP) Module XVI. EMA.

European Medicines Agency. (12. 09 2022). Dohvaceno iz EMA: https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/medication-errors

Jakubovic BD, D. A. (2013). Methotrexate-induced pulmonary toxicity. Canadian respiratory journal : journal of the Canadian Thoracic Society, 153-5.

(2019). PRAC Assessment report. EMA.

Saedder EA, B. B. (2014). Identifying high-risk medication: a systematic literature review. Eur J Clin Pharmacol, 637-45.

Shiver MB, H. L. (2014). Cutaneous erosions: a herald for impending pancytopenia in methotrexate toxicity. Dermatology online journal, 20(7).

Tan KW, T. Y. (2011). A case of acute methotrexate toxicity. Annals of the Academy of Medicine, Singapore., 97-9.