Annex II

Scientific conclusions

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Methotrexate is authorised in the European Union since the 1960s. 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 formulation 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 the PRAC to assess the root causes and the impact of the risk of medication errors on the benefit-risk balance of oral formulation 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.

The PRAC adopted a recommendation on 11 July 2019 which was then considered by the CHMP, in accordance with Article 107k of Directive 2001/83/EC.

Overall summary of the scientific evaluation by the PRAC

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)[1] 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[2]).

[1] Saedder EA1, Brock B, Nielsen LP, Bonnerup DK, Lisby M.:Identifying high-risk medication: a systematic literature review. Eur J Clin Pharmacol. 2014 Jun;70(6):637-45.
[2] Grissinger M. Severe Harm and Death Associated With Errors and Drug Interactions Involving Low-Dose Methotrexate. P T. 2018 Apr;43(4):191-248.

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 strengthen 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 (EMEA/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, implementation of educational material and patient card), should have a risk management plan (RMP) in place listing all pharmacovigilance activities and risk minimisation measures agreed.

To gain further knowledge on the reasons leading to medication errors and prevent them adequately, as well as in support of the measurement of the effectiveness of the agreed risk minimisation measures, all MAHs are requested to implement and use a targeted follow-up questionnaire, as agreed by PRAC, for all medication errors reported with methotrexate and resulting in overdose.

A direct healthcare professional communication was also agreed, together with a communication plan, to inform relevant healthcare professionals of the new recommendations and risk minimisation measures agreed.

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.

Grounds for PRAC 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.

CHMP opinion

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

The CHMP, as a consequence, considers that the benefit-risk balance of methotrexate-containing medicinal products remains favourable subject to the amendments to the product information and to the conditions described above.

Therefore the CHMP recommends the variation to the terms of the marketing authorisations for methotrexate-containing medicinal products.