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Committee for Medicinal Products for Human Use (CHMP)

Scientific conclusions and grounds for the variation to the terms of the marketing authorisation(s)

Active substance(s): methotrexate

Procedure No. EMEA/H/C/PSUSA/00002014/201706

Period covered by the PSUR: 29 March 2017 to 30 June 2017

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Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for methotrexate, the scientific conclusions of CHMP are as follows:

Methotrexate therapy for non-oncological indications follows a once weekly dosing regimen. Inadvertent daily instead of weekly dosing can potentially be fatal. Therefore, the product information should be updated. The warning about once weekly dosing should be more prominent in the product information (SmPC, PL and labeling).

Recent literature articles investigating the influence of low-dose methotrexate treatment on male fertility and pregnancy outcome after paternal exposure were not able to show an excess risk in malformation and miscarriage. The SmPC is updated to better reflect the current scientific knowledge.

A recent large prospective study investigated the cumulative risk for spontaneous abortion and major birth defects after exposure to low-dose methotrexate treatment (<30 mg/week). The SmPC is updated to reflect up-to-date information on pregnancy risks, pregnancy prevention, patient counselling, type of observed malformations and medical advice in the event of pregnancy.

The current statement that "*a recent study could not be established that methotrexate therapy increases the incidence of lymphomas*" should be deleted as such statement may create the impression that methotrexate is not associated with lymphoproliferative diseases/lymphomas.

A number of recent literature articles reported on methotrexate-related osteonecrosis of the jaw (ONJ) or lymphoproliferative disorder in patients with ONJ, and provided strong evidence for a causal effect of methotrexate for this ADR. The SmPC of methotrexate-containing products indicated in rheumatoid arthritis is updated to reflect this information.

Methotrexate and nitrous oxide both impair folate metabolism. Given the biological plausibility of this interaction, the SmPC of methotrexate-containing products is updated to reflect it and to indicate that concomitant use should be avoided.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for methotrexate the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing methotrexate is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.