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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/00002014/201910

Period covered by the PSUR: from 31 October 2018 to 31 October 2019

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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:

In view of the available data on medication errors due to handling issues resulting from lack of training with parenteral products suitable for self-administration the PRAC concluded that the product information (Section 4.2 of the SmPC and Section 3 of the PL) of products containing methotrexate suitable for parenteral self-administration by patients (i.e. prefilled syringes and prefilled pens) should be amended accordingly.

For products without any indication in oncology or extra-uterine pregnancy, the PRAC concluded that the existing wording in the product information (Section 4.5 of the SmPC) concerning the interaction between methotrexate and nitrous oxide should be amended to provide more clarity.

In view of available data on skin exfoliation from the literature, spontaneous reports, including in some cases a close temporal relationship, and a positive de-challenge and/or re-challenge, the PRAC considers that a causal relationship between methotrexate and skin exfoliation / exfoliative dermatitis is established. The PRAC concluded that an update of section 4.8 of the SmPC to add the adverse reaction "skin exfoliation / dermatitis exfoliative" with a frequency "not known" was warranted for all methotrexate containing products. The PL should be amended accordingly.

In view of available data on paraesthesia / hypoaesthesia (not restricted to extremities) from spontaneous reports, including in some cases a close temporal relationship, and a positive re-challenge, and existing product information the PRAC considers a causal relationship between methotrexate and paraesthesia / hypoaesthesia (not restricted to extremities) is at least a reasonable possibility.. The PRAC concluded that an update of section 4.8 of the SmPC to add or amend the adverse reaction "paraesthesia / hypoaesthesia" not restricted to the extremities with a frequency of "very rare" was warranted for low dose methotrexate-containing products. The PL should be amended accordingly.

In view of available data on oedema from spontaneous reports, including in some cases a close temporal relationship, and a positive de-challenge the PRAC considers a causal relationship between methotrexate and oedema is at least a reasonable possibility. The PRAC concluded that an update of section 4.8 of the SmPC to add the adverse reaction "oedema" with a frequency "not known" was warranted for low dose methotrexate-containing products. The PL should be amended accordingly.

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 products containing methotrexate is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the marketing authorisations should be varied.