Annex I

Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisation(s)

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.

Annex II

Amendments to the product information of the nationally authorised medicinal products

<Amendments to be included in the relevant sections of the Summary of Product Characteristics
(new text **underlined and in bold**, deleted text ~~strike through~~)>

Summary of Product Characteristics

Methotrexate-containing pre-filled syringes and pre-filled pens suitable for self-administration:

- Section 4.2

A statement should be included as follows:

Patients must be educated and trained in the proper injection technique when self-administering methotrexate. The first injection of [methotrexate containing product] should be performed under direct medical supervision.

Methotrexate-containing products without any indication in oncology or extra-uterine pregnancy:

- Section 4.5

The interaction should be amended as follows:

The use of nitrous oxide potentiates the effect of methotrexate on folate metabolism, yielding increased toxicity such as severe, unpredictable myelosuppression, and stomatitis. Whilst this effect can be reduced by administering calcium folinate, the concomitant use **of nitrous oxide and methotrexate** should be avoided.

All methotrexate-containing products:

- Section 4.8

The following adverse reactions should be added under the SOC “Skin and subcutaneous tissue disorders”:

“Skin exfoliation / dermatitis exfoliative” with a frequency “**not known”**

Low dose methotrexate-containing products:

- Section 4.8

The following adverse reactions should be amended under the SOC “Nervous system disorders”:

“Paraesthesia/hypoaesthesia ~~in the extremities~~**”** with a frequency of **“very rare”**

The following adverse reaction should be added under the SOC “General disorders and administration site conditions”:

“Oedema” with a frequency **“not known”**

<Amendments to be included in the relevant sections of the Package Leaflet (new text **underlined and in bold**, deleted text ~~strike through~~)>

Package Leaflet

Methotrexate-containing pre-filled syringes and pre-filled pens suitable for self-administration:

- 3. How to use <methotrexate-containing product>

At the start of your treatment, <methotrexate-containing product> may be injected by medical staff. However, your doctor may decide that you can learn how to inject <methotrexate-containing product> yourself. You will receive appropriate training for you to do this. Under no circumstances should you attempt to inject yourself, unless you have been trained to do so.

All methotrexate-containing products:

- 4. Possible side effects

"Not known: **redness and shedding of skin"**

Low dose methotrexate-containing products:

- 4. Possible side effects

"Very rare: **sensation of numbness or tingling / having less sensitivity to stimulation than normal** ~~in arms and legs"~~

"Not known: **swelling**"