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PRAC recommends updating measures for pregnancy prevention during retinoid use

Warning on possible risk of neuropsychiatric disorders also to be included for all oral retinoids

EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has concluded its review of retinoid[1] medicines and has recommended updating the measures for pregnancy prevention and including a warning on the possible risk of neuropsychiatric disorders (such as depression, anxiety and mood changes).

During its review, the PRAC assessed the available data including published literature and post-marketing reports of side effects, and also sought the views of patients and healthcare professionals in a dedicated stakeholder meeting and a successive written consultation. The PRAC recommendations are summarised below.

Pregnancy prevention

The PRAC confirmed that all oral (taken by mouth) retinoids can have harmful effects on the unborn child and therefore must not be used during pregnancy. In addition, the oral retinoids acitretin, alitretinoin and isotretinoin must not be taken by women able to have children unless the conditions of a pregnancy prevention programme (PPP) are met. Although PPPs for these retinoids were already in place in some EU Member States, the PRAC has now updated and harmonised the PPP to ensure it is optimal to support the discussion between the doctor and the patient on the risks of these medicines, and that it is followed in practice.

In particular, the new PPP includes assessing patients for the likelihood of becoming pregnant, requirements around pregnancy testing and the need for effective contraception before, during and after treatment, and ensuring that patients and prescribers go through an 'acknowledgement form' to confirm that appropriate advice has been given. Educational materials for doctors and a reminder card for patients will also be provided.

The companies that market acitretin, alitretinoin and isotretinoin will also conduct a study and a survey to assess the effectiveness of the updated measures, particularly to check how the PPP is implemented.

[1] Retinoids include the active substances acitretin, adapalene, alitretinoin, bexarotene, isotretinoin, tazarotene and tretinoin. They are taken by mouth or applied as creams or gels to treat several conditions mainly affecting the skin, including severe acne and psoriasis. Some retinoids are also used to treat certain forms of cancer.

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For the oral retinoids bexarotene and tretinoin a PPP was not considered necessary because these medicines, which are used to treat certain cancers, are used in a very different patient population under strict medical supervision and the current measures are considered appropriate for pregnancy prevention.

For topical (applied to the skin) retinoids, the data showed that the amount of active substance absorbed from the skin into the body is extremely low, and therefore these products are unlikely to cause harm to the unborn child. However, excessive use or skin lesions could possibly increase the absorption of retinoids. Therefore, as a precaution, the PRAC recommended that topical retinoids must also not be used during pregnancy and in women planning to have a baby.

Risk of neuropsychiatric disorders

The PRAC also reviewed the available data on the possible risk of neuropsychiatric disorders such as depression, anxiety and mood changes with retinoids. Although warnings about this possible risk were already included in the product information for some oral retinoids, the Committee reviewed the extent and nature of these warnings to ensure that they reflect the available evidence, and that they are applied consistently.

For oral retinoids, the PRAC noted the limitations of the available data, and considered that it could not be clearly established whether this risk was due to the use of these medicines. However, the PRAC recognised that patients with severe skin conditions may be more vulnerable to neuropsychiatric disorders due to the nature of the disease. The PRAC therefore recommended that the prescribing information for all oral retinoids should include a warning about this risk, including signs and symptoms patients and their families should be aware of (such as changes in mood or behaviour).

For topical retinoids, the available data, although extremely limited, suggest that these medicines do not carry a risk of psychiatric side effects and therefore no additional warnings need to be added to the prescribing information.

The PRAC recommendation will now be sent to the Committee for Medicinal Products for Human Use (CHMP), which will adopt the Agency's opinion. Further details including advice for patients and healthcare professionals will be published at the time of the CHMP opinion.

More about the medicines

Retinoids are vitamin A derivatives that are available as capsules to be taken by mouth or as creams and gels to be applied to the skin. Retinoids taken by mouth are used to treat various forms of severe acne, severe hand eczema that does not respond to treatment with corticosteroids, severe forms of psoriasis and other skin conditions, and certain types of cancer. Retinoids applied to the skin are used to treat various skin conditions including mild to moderate acne.

The following retinoids have been authorised nationally in a number of Member States of the EU and are covered by this review: acitretin, adapalene, alitretinoin, isotretinoin, tazarotene and tretinoin. Alitretinoin has also been authorised centrally as Panretin for the treatment of skin lesions in AIDS patients with Kaposi's sarcoma (a type of skin cancer). Bexarotene has been authorised centrally as Targretin for the treatment of the visible signs on the skin of cutaneous T-cell lymphoma (CTCL, a rare cancer of the lymph tissue).

More about the procedure

The review of retinoid medicines was initiated on 8 July 2016 at the request of the United Kingdom, under Article 31 of Directive 2001/83/EC.

The review has been carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which has made a set of recommendations. The PRAC recommendations will now be sent to the Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which will adopt the Agency's opinion. The final stage of the review procedure is the adoption by the European Commission of a legally binding decision applicable in all EU Member States.