Annex II

Scientific conclusions

Scientific conclusions

On 7 July 2016 the United Kingdom triggered a referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data, and requested the PRAC to review the routine risk minimisation measures in place for the oral and topical retinoids to ensure the available data and the risks associated with the adverse teratogenic effects and neuropsychiatric disorders are accurately and consistently addressed within the product information where appropriate and justified by data. Furthermore, the PRAC was requested to review any additional risk minimisation measures to ensure that these are optimal in terms of provision of information and delivery of effective risk management that is subject to appropriate monitoring. The PRAC was requested to assess the impact of the above concerns on the benefit-risk balance of retinoid-containing medicinal products and issue a recommendation on whether the products should be maintained, varied, suspended or revoked.

After reviewing all the available data to address the concerns discussed, the PRAC adopted a recommendation on 8 February 2018 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 PRAC reviewed all available data from pre-clinical studies, pharmacovigilance data, published literature and spontaneous reports on the risks associated with the adverse teratogenic effects and neuropsychiatric disorders of oral and topical retinoids. In addition, the views of patients and healthcare professionals regarding communication, awareness and understanding of the risks of retinoids during pregnancy and in women of childbearing potential were taken into account in the recommendation along with their views on options for improving risk communication.

The review confirms the already known teratogenic risks associated with the use of oral retinoids in pregnant women. The data suggest that the risk of adverse pregnancy outcomes is more strongly associated with the oral retinoids than the topical retinoids. The animal reproductive toxicity data for the oral retinoids demonstrate a typical pattern of retinoid embryopathy. The human data on congenital malformations after oral retinoid exposure show a significant risk of retinoid embryopathy (of up to 30% of fetuses exposed); furthermore it is known that approximately one-third of pregnant patients exposed to oral retinoids during pregnancy will have spontaneous abortions. Pregnancy is an absolute contraindication for all oral retinoids in the EU.

The PRAC noted that despite the introduction of pregnancy prevention measures, including pregnancy prevention programmes (PPPs), cases of pregnancy during treatment with oral retinoid continue to be reported in the EU.

Compliance with the PPP is crucial to a positive benefit/risk balance for these products; therefore, the adequacy of the pregnancy prevention measures, including PPPs, for the oral retinoids acitretin, alitretinoin and isotretinoin has been reviewed to ensure that the available materials effectively encourage contraception use, regular pregnancy testing and shared responsibility between patients, doctors and pharmacists in adhering to recommendations, and that this is communicated consistently and effectively for all products. Furthermore, specific studies to measure effectiveness of the agreed changes to the PPP have been imposed on the marketing authorisation holders as an outcome of the referral.

In this respect, the PRAC recommended amendments to the product information, including harmonising the warnings and precautions of use for the oral retinoids acitretin, alitretinoin and isotretinoin to reflect the teratogenic risk associated with their use and communication to healthcare professionals through a direct healthcare professional communication. In addition, the PRAC recommended changes to the educational materials for the oral retinoids (acitretin, alitretinoin and isotretinoin) to ensure healthcare professionals and patients are informed about the risks associated with oral retinoids (acitretin, alitretinoin

and isotretinoin) in pregnant women and women of child-bearing potential and on the measures necessary to minimise the risk. These include a patient reminder card, physician checklist/acknowledgement form and pharmacist checklist ensuring the understanding and the awareness of prescribers and patients on the risks. The PRAC has also recommended that educational materials be distributed via electronic channels such as QR codes, and websites to make better use of the existing technology bearing in mind the young patient population using these products.

The PRAC acknowledged that the implementation of the following elements of the PPP need to be considered and agreed at national level to account for the different healthcare systems in the EU:

- The implementation of the 7-day prescription validity rule, in order not to impact on existing national legislation where 7 days validity exists;
- Patient signature of the physician checklist/acknowledgement form;
- Dissemination of the patient reminder card;
- Pharmacist checklist;
- Inclusion of appointment table in the patient reminder card;
- The option of a pictogram/symbol to accompany the box warning wording and to be included in the visual reminder on the outer package to warn patients about the harm to unborn baby and the need for effective contraception when using the medicinal product.

PRAC considered that given the oncological indications of oral tretinoin and oral bexarotene, further risk minimisation measures (RMMs) for these products regarding teratogenic effects, such as strengthening the product information (PI) and additional risk minimisation measures (aRMMs) would not provide an added value given the specialist management, the population at risk and the nature of the illness.

The PRAC noted the systemic exposure is negligible following topical application of retinoids and that this does not appear to be affected to a clinically significant degree by the severity or extent of skin disease. Studies that examine the effects of human pregnancy on systemic absorption of topical retinoids are also lacking. However, there was a consensus that several other factors may contribute to an increased systemic exposure and therefore the risk cannot be excluded.

Given that humans are the most sensitive species with respect to retinoid toxicity and considering the limitations of the available data with respect to understanding the systemic absorption and also the possible risks, the PRAC, considers that it is appropriate to take a very precautious approach. The indications for the topical retinoids are non-life-threatening and there is no absolute clinical need for the treatment during pregnancy and pregnancy should be excluded before prescribing. The PRAC thereby concludes that the benefit-risk balance of topical retinoids in pregnancy is not favourable, and therefore recommends that use of topical retinoids should be contraindicated during pregnancy and in women planning a pregnancy.

The PRAC recognizes that the available data in relation to oral retinoids and the occurrence of neuropsychiatric disorders have a number of important limitations that preclude the establishment of a clear causal association. Nevertheless, the PRAC considers that the data from patients presented in case series, spontaneous case reports and individual patients' experiences are considered to be very important. Although the underlying risk of psychiatric disorders within the patient populations can be significant, it is advisable that patients taking oral retinoids are warned about the potential risk of psychiatric reactions and the signs and symptoms to look out for. Therefore, the PRAC agrees that all oral retinoids should contain a warning about the potential risk of neuropsychiatric disorders in line with some key principles. The data support that for isotretinoin and alitretinoin the information in section 4.4 and 4.8, of the SmPC, should be in line with the agreed outcome of the 2003 Art 30 referral for isotretinoin.

The PRAC further noted the extremely limited data relating to neuropsychiatric reactions after topical administration of retinoids. Given this and the negligible systemic exposure following topical no further risk minimization activities are deemed necessary.

Overall, the PRAC concludes that the benefit-risk balance of medicinal products containing retinoids remains favourable, but that marketing authorisation(s) should be varied for both the oral and topical retinoids to ensure risks associated with the adverse teratogenic effects and neuropsychiatric disorders are accurately and consistently addressed, as appropriate.

Grounds for PRAC recommendation

Whereas,

- The Pharmacovigilance Risk Assessment Committee (PRAC) considered the procedure under Article 31 of Directive 2001/83/EC for retinoid-containing medicinal products.
- The PRAC considered the totality of the data submitted, including responses from the marketing authorisation holders with regard to the consistency and effectiveness of existing routine and additional risk minimisation measures for oral and topical retinoids-containing medicinal products in relation to teratogenic effects and neuropsychiatric disorders. In addition, the PRAC considered the views of patients and healthcare professionals in relation to their understanding and the awareness of the teratogenic risk associated with the use of retinoid-containing medicines.
- With regards to the teratogenic risk, the PRAC confirmed that all oral retinoids (acitretin, alitretinoin, bexarotene, isotretinoin and tretinoin) are highly teratogenic and therefore must continue to be contraindicated during pregnancy or in women of child bearing potential unless they are using effective contraception. Given the indications and patients populations that use acitretin, alitretinoin and isotretinoin, it was considered that any use of these oral retinoids in female patients at risk of pregnancy must be in accordance with the conditions of a pregnancy prevention programme (PPP). For tretinoin and bexarotene, it was considered that in light of the oncological indications, specialist management in a hospital setting and population at risk that existing risk minimisation was appropriate and proportionate.
- The PRAC also concluded that there was a need to further harmonise and streamline the measures in the PPP including associated educational materials for the oral retinoids acitretin, alitretinoin and isotretinoin to ensure these are optimal to support discussions between patients and healthcare professionals on the risks and the associated risk minimisation measures.
- The PRAC further considered that for the oral retinoids acitretin, alitretinoin and isotretinoin a drug utilisation study with a complementary survey should be conducted to assess the effectiveness of the proposed updated risk minimisation measures.
- A direct healthcare professional communication (DHPC) was also considered appropriate for all oral and topical retinoids.
- With regards to the teratogenic risk of topical retinoids (adapalene, alitretinoin, isotretinoin, tretinoin and tazarotene), the PRAC concluded that the data available show that after topical application, systemic exposure is expected to be negligible and unlikely to result in adverse fetal outcomes. However, given that humans are the most sensitive species to retinoid embryopathy and that several other factors may contribute to an increased systemic exposure, such as excessive use and damaged skin barrier, the PRAC agreed that the teratogenic risk cannot be completely excluded. The PRAC therefore recommended that the use of topical retinoids should be contraindicated during pregnancy and in women planning a pregnancy given the non-life threatening nature of the indications.

- With regards to neuropsychiatric disorders, the PRAC noted the limitations of the available data and considered that a clear causal relationship could not be established with the oral retinoids. However, taking into account the target patient population, the PRAC recognised the possible underlying risk of psychiatric disorders, and therefore recommended some changes to the product information such as warnings and precautions and so that the current level of available evidence is appropriately reflected.
- Furthermore, the PRAC noted the extremely limited data relating to neuropsychiatric reactions after topical administration of retinoids. Given this and the negligible systemic exposure following topical use, the PRAC considered that no further risk minimization activities are deemed necessary.

In view of the above, the PRAC considers that the benefit-risk balance of retinoid-containing medicinal products remains favourable subject to the agreed amendments to the product information and risk management plan, the conditions to the marketing authorisations and the related communication.

The PRAC, as a consequence, recommends the variation to the terms of the marketing authorisations for retinoid-containing medicinal products.

CHMP opinion

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

The CHMP clarified that the communication plan should be modified to say ‘healthcare professionals who may be involved in the management of patients treated with retinoids’.

Overall conclusion

The CHMP, as a consequence, considers that the benefit-risk balance of retinoid-containing medicinal products remains favourable subject to the agreed amendments to the product information and risk management plan, the conditions to the marketing authorisations and the related communication.

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