7 July 2016
EMA/PRAC/461926/2016

PRAC List of questions

To be addressed by the marketing authorisation holder(s) for Retinoids containing medicinal products

Referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Procedure number: EMEA/H/A-31/1446

Panretin EMEA/H/A-31/1446/C/000279/0037
Targretin EMEA/H/A-31/1446/C/000326/0043

INN: Acitretin, Adapalene, Alitretinoin, Bexarotene, Isotretinoin, Tretinoin, Tazarotene

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Background

Retinoid-containing medicinal products are available in oral and topical forms and are authorised both centrally and nationally. They are widely used to treat a variety of conditions mainly affecting the skin such as various forms of acne, severe chronic hand eczema unresponsive to corticosteroids, severe forms of psoriasis and keratinisation disorders. Tretinoin may also be used to treat promyelocytic leukaemia.

Retinoids are recognised to be teratogenic at the recommended therapeutic dose of the oral formulations. The main known teratogenic effects are central nervous system, craniofacial, cardiovascular and thymic abnormalities. Oral retinoid products have been associated with reports of significant neuropsychiatric adverse reactions such as depression, anxiety, psychotic disorder, suicidal ideation, suicide attempt and suicide.

Pregnancy is an absolute contraindication in the SmPCs for all oral retinoids in the EU. A referral in 2003 for isotretinoin only, led to introduction of the isotretinoin pregnancy prevention programme (PPP) in the EU. Since the introduction of the PPP for isotretinoin, similar programmes have been introduced for the other retinoids used to treat dermatological conditions. The effectiveness of these PPPs has been kept under close review and although a reduction in the number of pregnancies exposed to these retinoids has been observed, cases of pregnancies exposed to retinoids continue to occur.

In January 2016 the PRAC reviewed the effectiveness of the PPP for oral isotretinoin. This review noted post-marketing data and published studies raising concerns about how well the requirements of the PPP are followed in clinical practice. These data suggested that there were a number of areas that may impact on the effectiveness of the PPP including inconsistencies in information provided with regard to contraceptive measures and a lack of up-to-date information about the most effective contraceptive methods; inadequate documentation of the required patient monitoring; and potential differences in the pregnancy prevention programmes implemented across the generics. Consequently the PRAC identified a need for a detailed assessment of compliance with the requirements of the PPP for isotretinoin. Subsequent discussions in the context of the PSUSAs for erythromycin plus isotretinoin topical gels and of acitretin, have also highlighted that there are concerns about the consistency and effectiveness of existing risk minimisation measures for these products.

Information gathered from NCAs has confirmed the need to review product information and risk minimisation measures across the retinoid class. This data showed that the majority but not all topical retinoids include a contraindication for use during pregnancy and that there are inconsistencies between products with the same active substance and between member states (MS) as to the extent of the warnings and the risk minimisation measures in place for pregnancy prevention. In particular, the majority of MS only have additional risk minimisation material for oral isotretinoin products.

With regard to the possible risk of neuropsychiatric disorders with retinoids, the extent to which the association is attributable, and the magnitude of any risk is unclear. However, there have been warnings in the isotretinoin product information for many years reflecting a risk of neuropsychiatric disorders and highlighting the need for patients to be monitored. Although the issue has been subject to extensive reviews at Member State level it has not been subject to formal review at EU level since 2006. Consequently, there are differences in the extent and the nature of warnings about neuropsychiatric reactions that exist within the isotretinoin product information. Other oral retinoids have similarly been associated with neuropsychiatric reactions and it would be important to consider whether appropriate warnings are provided for all retinoids and whether any additional risk minimisation measures are required.

In conclusion, there is a need to thoroughly review the routine risk minimisation (warnings in the SmPC and package leaflet) 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, it is necessary 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.

Based on the above and the necessity to take action at EU level, the UK considered it was in the interest of the Union to refer the matter to the Pharmacovigilance Risk Assessment Committee, and requestee that PRAC gives its recommendation under Article 31 of Directive 2001/83/EC, on whether the marketing authorisations of these products should be maintained, varied, suspended, or revoked.

1. Questions

The marketing authorisation holders MAH(s) are requested to address the following questions:

Question 1

Please provide information on a) pregnancy prevention and b) neuropsychiatric reactions for the currently authorised medicinal products containing acitretin, adapalene, alitretinoin, bexarotene, isotretinoin, tretinoin and tazarotene in the different EU Member States. The information should be provided in the form of separate tabulated summaries (see Annex 1).

In addition, for each active substance and route of administration, please provide estimated usage in each EU Member State. Where possible, the information on usage should include:

i. A yearly breakdown of sales and exposure over the last 10 years for each Member State. Please provide an explanation as to how the estimated exposure has been calculated.

ii. A breakdown of use in girls and women of child bearing potential (women between 12 and 49 years) for each Member State.

Question 2

In relation to the teratogenic risk associated with exposure during pregnancy, please provide a critical analysis of the following data for your product:

a) Pre-clinical data;

b) Completed or ongoing interventional studies;

c) Epidemiological studies;

d) Published literature;

e) Data from spontaneous case reports including a breakdown of the pregnancy cases with pregnancy outcome and offspring status for:

   i. conception occurring prior to starting treatment and the pregnancy subsequently being exposed;
   ii. conception occurring during treatment;
   iii. conception occurring after completing treatment within the at risk period defined within the SmPC;
   iv. pregnancies occurring where the time of exposure was unknown.

The critical analysis should evaluate the available evidence, including the nature and magnitude of the teratogenic risks, to establish whether they are accurately reflected by the current risk minimisation activities and whether these measures are proportionate to the risk.

Question 3

For topical products, please provide a review of the available evidence regarding systemic absorption. The evidence of systemic exposure should include any comparisons with levels obtained from relevant authorised oral products and background levels from the diet.

Question 4

In relation to compliance and the effectiveness of the pregnancy prevention measures information is required for each product in each EU Member State. Please provide a tabulated summary (see Annex 1) of the requested information as well as a critical analysis of the available data.

The critical analysis should evaluate the available evidence to establish whether the risk minimisation measures defined, effectively aid patient and prescriber understanding of the teratogenic risk, and are monitored appropriately. Please provide proposals and justifications for any updates to these risk minimisation measures which may improve the benefit/risk balance of your product(s).

Question 5

In relation to the risk of neuropsychiatric disorders, please provide a critical analysis of all available safety data including:

a) Completed or ongoing interventional studies in the clinical development programme

b) Epidemiological studies

c) Meta-analyses and systematic reviews

d) Published literature

e) Spontaneous case reports

The critical analysis should evaluate the available evidence to establish the possible risks of neuropsychiatric reactions associated with the product and whether a causal association can be determined and if there are particular at risk groups.

Consideration should be given to whether further risk minimisation would be required in specific populations at risk, such as in relation to gender, age, previous psychiatric history, duration of retinoid treatment.

Question 6

In light of the responses to the questions above, please provide a discussion of the impact of the risks of teratogenicity and neuropsychiatric disorders on the benefit/risk balance of your product. This should also include:

a) a discussion of the adequacy and proportionality of the existing risk minimisation measures (including changes to the SmPC/PL or additional educational material);

b) proposals and justifications for any updates to these risk minimisation measures which may improve the benefit/risk balance of your product(s). If no risk minimisation measures or amendments to existing risk minimisation measures are deemed necessary, justification should be provided;

c) details of how the effectiveness of these risk minimisation measures will be monitored.

Annex 1

Question 1a)

INNs	Product name	Route of administration	Indication	Details of contraindications and warnings on pregnancy prevention in SmPC and package leaflet	Description of any additional pregnancy prevention measures	Any differences between the product information in the different EU member states

Question 1b)

INNs	Product name	Route of administration	Indication	Details of warnings about neuropsychiatric reactions in SmPC and package leaflet	Description of any additional measures to minimise risk of neuropsychiatric reactions	Any differences between the product information in the different EU member states

Question 4

Member State	Product details (name and route of administration)	Overview of the materials to support the PPP	Summary of distribution of PPP materials	Date materials last updated or reviewed	Details of last amendment to the PPP materials	Data regarding compliance with the PPP requirements	Methods used to monitor the effectiveness of the PPP