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Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

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

Retinoids containing medicinal products

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

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

Note:

Assessment report as adopted by the PRAC and considered by the CHMP with all information of a commercially confidential nature deleted.

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1. Information on the procedure

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 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 its recommendation on 8 February 2018 that will be sent to the Committee for Medicinal Products for Human Use (CHMP).

2. Scientific discussion

2.1. Introduction

Retinoids are natural or synthetic vitamin A derivatives with pleiotropic effects that regulate cell differentiation, proliferation and apoptosis. First-generation retinoids include retinol tretinoin (all-trans-retinoic acid) isotretinoin (13-cis-retinoic acid) and alitretinoin (9-cis-retinoic acid). Second-generation retinoids also known as aromatic retinoids were created by alteration of the cyclic end group and include acitretin. Third-generation retinoids contain further modifications and are called arotinoids. Members of this generation include tazarotene and bexarotene. Adapalene a derivative of naphthoic acid with retinoid-like properties does not fit precisely into any of the three generations.

Pregnancy is an absolute contraindication in the SmPCs for all oral retinoids in the EU. A referral in 2003 for isotretinoin led to introduction of a pregnancy prevention programme (PPP) in the EU. Since the introduction of the PPP for isotretinoin similar programmes have been introduced for the other oral 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, in the context of a Periodic Safety Update Report single assessment (PSUSA) procedure, the PRAC raised concerns about how the requirements of the PPP are followed in clinical practice, identifying areas that may impact on the effectiveness of the PPP. 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 was gathered from NCAs through a Non-Urgent Request for Information (NUI) showing 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, between oral and topical retinoids products and between Member States (MS) as to the extent of the warnings and the risk minimisation measures in place for pregnancy prevention, confirmed the need to review product information and risk minimisation measures across the retinoid class to ensure those are accurately and consistently addressed within the product information.

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. New evidence has been evaluated as it has become available and, although subject to extensive reviews at MS level, it has not been subject to formal review at EU level since 2006. The product information (PI) for isotretinoin reflects a potential risk of neuropsychiatric disorders and highlighting the need for patients to be monitored. However, 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 in the product information are provided for all retinoids and whether any additional risk minimisation measures are required.

Consequently, 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 in place for the oral and topical retinoids to assess the impact of the above concerns on the benefit-risk balance of these products and issue a recommendation on whether their marketing authorisation should be maintained, varied, suspended or revoked.

The following table presents the substances which have been reviewed in the context of this referral, with their approved indications:

ORAL RETINOIDS	TOPICAL RETINOIDS
Acitretin: Severe extensive psoriasis which is resistant to other forms of therapy; palmo-plantar pustular psoriasis; severe congenital ichthyosis; severe Darier's disease (keratosis follicularis)	**Adapalene:** Topical treatment of acne vulgaris where comedones, papules and pustules predominate
Alitretinoin: For use in adults who have severe chronic hand eczema that is unresponsive to treatment with potent topical corticosteroids	**Alitretinoin:** Topical treatment of cutaneous lesions in patients with AIDS-related Kaposi's sarcoma (KS) when lesions are not ulcerated or lymphoedematous, and treatment of visceral KS is not required, and lesions are not responding to systemic antiretroviral therapy, and radiotherapy or chemotherapy are not appropriate
Isotretinoin: Severe forms of acne (such as nodular or conglobate acne or acne at risk of permanent scarring) resistant to adequate courses of standard therapy with systemic anti-bacterials and topical therapy	**Isotretinoin:** Topical treatment of mild to moderate, inflammatory and non-inflammatory acne vulgaris
Bexarotene: Treatment of skin manifestations of advanced stage cutaneous T-cell lymphoma (CTCL) in adult patients refractory to at least one systemic treatment	**Tazarotene:** Topical treatment of mild to moderate plaque psoriasis involving up to 10% body surface area.
Tretinoin: Treatment of genetically diagnosed acute promyelocytic leukaemia (APL)	**Tretinoin:** Topical treatment of acne vulgaris when comedones, papules and pustules are present in patients 12 years or older

PRAC considered the totality of the available data, including responses from marketing authorisation holders, submitted with regard to the consistency and effectiveness of existing routine and additional

risk minimisation measures for oral and topical retinoid containing medicinal products in relation to adverse teratogenic effects and neuropsychiatric disorders. In addition, PRAC considered the views of patients and healthcare professionals for the understanding and the awareness of the teratogenic risk associated with the use of retinoid-containing medicines. The following report summarises the most relevant data.

2.2. Clinical aspects

2.3. Data on efficacy

The efficacy of oral and topical retinoids in their authorised indication(s) has been well established and is detailed in each product information. The aim of this referral procedure was specifically to address questions related to the safety of retinoid containing medicines and no questions were asked in relation to the efficacy of these products. No new efficacy data have been provided for this referral procedure by the MAHs and no efficacy concerns arose from the assessment of the data presented.

2.4. Data on safety

2.4.1. Teratogenic effects – oral retinoids

The teratogenic effects of oral vitamin A derivatives are well established (Nau H., at al (2001)) and patients treated with these drugs may include women of child-bearing potential (WCBP) (Lipson AH, at al. (1993). Retinoic acid embryopathy include central nervous system abnormalities (hydrocephalus, microcephaly), external ear abnormalities (anotia, microtia or absent external auditory meatus), cardiovascular abnormalities (septal wall and aortic defects), facial dysmorphia (cleft palate), eye abnormalities (microphthalmia), thymus gland and bone abnormalities (Lipson AH, at al. (1993).

The data suggest that the risk of adverse pregnancy outcomes is more strongly associated with the oral retinoids than the topical retinoids (Raguideau, F., at al. (2015)). Animal reproductive toxicity data for the oral retinoids demonstrate a typical pattern of retinoid embryopathy (Johnson EM., at al (1997)). Human data on congenital malformations after oral retinoid exposure shows a significant risk of retinoid embryopathy (of up to 30% of foetuses exposed); furthermore it is known that approximately one-third of pregnant patients will undergo spontaneous abortions (Nau H., at al (2001)). Pregnancy is an absolute contraindication for all oral retinoids in the EU.

In 2003, as a conclusion to an Article 30 of Directive 2001/83/EC referral, it was agreed that oral isotretinoin should only be prescribed to WCBP under strict pregnancy prevention measures supported by a Pregnancy Prevention Programme (PPP). Pregnancy prevention measures, including Pregnancy Prevention Programmes have been implemented by marketing authorisation holders of different oral retinoids products, albeit inconsistently and with different levels of information.

Despite the introduction of PPPs for some products, cases of pregnancy during treatment with oral retinoids continue to be reported in the EU. Several studies have considered the effectiveness of the PPP for isotretinoin and several publications describe poor compliance particularly with the pregnancy testing and use of contraception (Crijns, H. J., et al. (2012); Veyries, M. (2015); Henry, D., et al. (2016)).

Concerning acitretin, a cohort study (Raguideau, F., et al. (2015)) conducted in France between 2007 and 2012 also highlighted concerns about poor compliance with pregnancy testing requirements for acitretin.

The number of pregnancies since the date of first marketing, as presented by the MAHs, was assessed cumulatively and respectively as follows:

- Acitretin: 442 pregnancy cases (132 related to conception during treatment, 260 after completing treatment);
- Alitretinoin: 17 pregnancy cases (12 related to conception during treatment, 4 more than one month after stopping treatment);
- Isotretinoin: 7968 pregnancy cases from all sources (the majority of cases from USA).

These data however are considered to be largely underestimated because of the limitations of the pharmacovigilance system which is not designed to collect pregnancy occurrence.

Unfortunately the majority of cases reporting malformations lack information regarding contraceptive measures, which makes it difficult to assess patient adherence to recommendations.

Compliance with the PPP is crucial to a positive benefit/risk balance for these products in women of child-bearing potential; therefore, the adequacy of the existing pregnancy prevention measures for the oral retinoids acitretin, alitretinoin and isotretinoin has been reviewed in order to ensure that the available materials effectively encourage use of contraception, regular pregnancy testing and shared responsibility between patients, doctors and pharmacists in adhering to recommendations, and that this is done consistently and effectively for all products. Further consideration has also been given to the package labelling to reinforce key messages. 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.

Considering the particular oncological indications of oral tretinoin and oral bexarotene, further risk minimisation measure (RMM) for these products regarding teratogenic effects might be seen as an extra and unnecessary burden for patients and healthcare professional (HCPs). For these particular populations, strengthening the product information (PI) and additional risk minimisation measure (aRMM) would not provide an added value given the specialist management, the population at risk and the nature of the illness. In particular, oral tretinoin is used in the context of a life-threatening illness that will be subject to specialist care in the hospital setting and oral bexarotene is indicated for use in a patient population that is generally not of reproductive age.

Adequacy of existing PPP and proposals for updates

Pregnancy prevention programme (PPP) materials, which clearly convey the risks and the importance of strict adherence to the pregnancy prevention measures, are essential to reinforce the communication between HCP and patients. Real patient engagement and consequently greater compliance with the PPP can only be achieved with a clear exchange of information.

Where oral retinoids currently have PPPs, the PPP materials are known to be inconsistent between the different active substances and also between products containing the same active substance. To this effect, PRAC agreed that the material should be simplified and harmonised across active substances and be tailored to each type of recipient, i.e. patients, physicians and pharmacists, and include the following set of key messages:

a. Teratogenicity risk – what it means to the unborn fetus;
b. Contraception – understanding the 'risk period', and what measures need to be observed during this risk period;
c. Pregnancy testing – why this is important, and why ideally 30-day prescriptions are required.

The patients and healthcare professionals consulted during the procedure indicated that specialists managing patients who take oral retinoids are experienced in the use of these products. It was therefore agreed that the materials should be simplified with the key objective of best supporting discussions without providing unnecessary information that physicians are already aware of or can access from other sources such as the SmPC.

Some key components of the PPP and the different elements of the additional risk minimisation measures, including a discussion on the use of different electronic dissemination channels, are presented below:

30-day prescription requirement

The aim of this referral procedure was to enhance compliance with the PPP to guarantee patient safety, however, it is recognized that any obligations of the PPP need to be workable in clinical practice and in this respect need to provide for an element of clinical discretion based on the individual circumstances of the WCBP. The PPP conditions should also be practicable in relation to the different MS healthcare system practices. The importance of this was reinforced through the consultation with the HCP and patient stakeholder group who considered that restrictive conditions such as those of the iPLEDGE PPP for isotretinoin in the USA should be avoided.

Several elements of the PPP such as the feasibility of monthly follow-up visits, monthly medically supervised pregnancy testing, the limitation of the prescription to a 30-day supply and the 7-day prescription validity, are known to be a challenge in some MS. Furthermore, the differences in MS healthcare systems will greatly influence how viable it is to implement each of these conditions. Lastly, the woman's individual circumstances also need to be evaluated in order to determine the optimal approach to follow-up and monitoring. Therefore, whilst it was recognised that there should be regular follow-up, which ideally should be on a monthly basis, there may be situations where this is not absolutely essential (e.g. WCBP who is established on a highly effective form of contraception such as an implant or intrauterine device). Therefore, it was considered that the conditions of the PPP should provide an element of clinical discretion with regards to the prescription duration according to the patient's situation and risk of becoming pregnant.

In order to minimize the risk for the unborn child it is crucial to detect an eventual pregnancy under treatment as early as possible and this can only be achieved if pregnancy tests are performed regularly. Consequently, follow-up visits should be arranged at regular intervals, and to support this regular follow-up, the prescription duration should ideally be limited to 30 days but it is recognized that flexibility might be necessary.

7 day-prescription validity

The 7-day prescription validity was introduced as a result of the 2003 isotretinoin Art. 30 referral. The original intention of this was to encourage patients to obtain their prescription in a timely manner so that the results of the pregnancy test remained valid and that dispensing occurred as close as possible to such testing.

Healthcare professionals and several MS have highlighted that this measure could not always be ensured at pharmacy level; moreover imposing 7 days may not be in line with the national legal validity of medical prescriptions in some MS.

It is essential that the initial pregnancy test is performed correctly to exclude a pregnancy and that contraception is initiated immediately thereafter; the initiation of retinoid treatment immediately after

the pregnancy test however is not critical. Any measures in this respect need to be practicable, considering the possible differences between Member State healthcare systems and legislation.

In light of all the above considerations, the PRAC was of the opinion that the product information and educational materials key messages will not specify the 7 day validity of the prescription across the EU. The PRAC acknowledged, however, the differences between healthcare systems in the EU, where in some member states the 7 days validity rule is already in place. PRAC was of the opinion that national provisions different than the PI and the educational material key messages could be retained, subject to the NCA scrutiny.

Two forms of contraception

The requirement for two forms of contraception was discussed during the referral and it was considered whether taking further measures to strengthen the requirements of the PPP in this respect would necessarily lead to enhanced compliance. It was stressed that individual circumstances should always be evaluated in each case. Additionally, it was recognized that imposing two forms of contraception may not have the desired effect as two methods with poor compliance (e.g. condom with CHC) are by definition not safer than appropriate use of one highly effective method (e.g. intra-uterine device). Therefore, the PRAC agreed that a user-independent method such as an implant or an intrauterine device is the preferred contraceptive option and that updates to the SmPC and PL and educational materials were required to clarify this.

Medically supervised pregnancy testing

The first pregnancy test, prior to the first prescription needs to be medically supervised. Thereafter, where indicated, follow-up pregnancy tests should be performed on the day of the prescribing visit or in the 3 days prior to the visit to the prescriber. This allows for appropriate clinical discretion but guarantees that patients will get their prescription in a timely way in order that the results of the pregnancy test remain valid.

A pregnancy test needs to be performed at a specified time period following the end of treatment, which is determined based on the metabolism of the product and is one month for alitretinoin and isotretinoin and 3 years for acitretin.

Educational materials

The following table presents the agreed changes to the documents constituting the PPP educational materials (EM) (please see enclosure 5):

	Previous educational materials	Final agreed educational materials
Patient materials	*Patient brochure and Contraception advice brochure*	*Patient reminder card* Objectives: a) support discussion with HCP; b) act as a reminder and support discussions at dispensing level; c) present the key principles of the PPP; d) to record visits, pregnancy test results and contraception method by means of an appointment table*.

	Previous educational materials	Final agreed educational materials
		**Inclusion of appointment table will be left at the discretion of MS.*
Physician materials	*Physician guide, Physician checklist and Acknowledgement form*	*Physician checklist/acknowledgement form* Objectives: a) support discussions with patient; b) present the key principles of the PPP; c) to record* that those discussions have taken place. **Implementation of the signature will be left at the discretion of the MS.*
Pharmacist materials	*Pharmacist brochure*	*Pharmacist checklist** Objectives: a) support pharmacist assessment of PPP obligations; b) to instruct patients not to share medicine with others; to return unused medicine and not to donate blood. **The implementation of the pharmacist checklist will be left at the discretion of the MS.*

Patient Reminder Card (PRC)

A patient reminder card will be required with the ultimate goal of supporting discussions at the level of prescribing and dispensing, thereby improving adherence to the PPP. The PRAC and stakeholders discussed in particular the content, placement and distribution of the PRC to achieve this goal. There was no consensus from the stakeholders on that point. The card given by the prescriber will act as an useful reminder of the key elements of the discussions. Having the PRC given with each package would guarantee that every patient receives a card and placing it on the outside of the pack means it could be easily removed and therefore could also support the discussion with the pharmacist at the time of dispensing. However, in itself this does not guarantee that it is seen and read by the patient as it cannot be guaranteed that the patient will read the PL or PRC. Also, having the card on the outside of the package will mean that patients receive multiple cards with every new package, even if they are not the target population, such as men or women with no chance to get pregnant.

The PRC brings together all the relevant information for the patient and will be of a small size, allowing it to be carried by the patient on a daily basis.

The provision of the PRC to patients (e.g. by the physician, inside the pack, outside the pack, the method of dissemination etc.) should ensure that this material supports clear discussions about the treatment. In light of different healthcare practices across the EU, the PRAC agreed that these aspects of the implementation in each MS is to be determined by the respective competent authority. The

agreements at national level should always be made with the aforementioned goal in mind of how best to support HCP-patient discussion.

The utility of including an appointment table in the PRC was discussed, with stakeholders questioned on this point. There was no consensus from the stakeholders on that point. Although it was noted to be of potential use by some, it was also mentioned that in some MS appointments are made via texts and phone calls. In view of these reflections, the PRAC concluded that the decision to include an appointment table to register dates and test results should be left at the discretion of the national competent authority taking due consideration of the existing local practices.

Prescriber and pharmacist checklists

The materials for HCPs (physician and pharmacist) in the form of checklists are designed to enhance conversation with the patients and understanding of the PPP requirements, and increase the level of engagement with the PPP. The materials also serve as a reminder to align HCP involvement and focus on patient's compliance.

The key elements of the physician checklist were agreed by the PRAC (please see enclosure 5); however, the decision as to whether or not the checklist should include a signature should be left to the discretion of MS in order to account for the differences in healthcare practices across the EU. The physician checklist/acknowledgement form will be easily recorded and accessible in the patient files for future reference.

The pharmacist checklist is common to all oral retinoids with a PPP in place; its implementation is to be agreed by each relevant competent authority.

Distribution of educational materials

Materials should be available both in paper and electronically.

Website/URL

The benefits of having the PPP materials available online are generally acknowledged, and some MAHs already use their own websites to provide product information, but the amount of information provided differs between MAHs.

Although there is no existing legal framework to enable the PRAC to impose the development of a common website, the PRAC strongly recommends that a common website be created which would contain the PPP materials for the oral retinoids acitretin, alitretinoin and isotretinoin. This would help to keep the pregnancy prevention message consistent across all products and prevent any confusion from differences in individual MAH materials.

QR Code

Quick Response (QR) codes are a type of 2D matrix barcode. QR codes can be scanned by devices such as smart phones and can be used as a quick link to URLs, images, music or videos. Article 62 of Directive 2001/83/EC allows for the inclusion of QR codes for the purpose of providing information to patients. The QR code could be included on either the outer packaging or on the package leaflet.

The PRAC recognises that there are some limitations to the use of QR codes, such as their use by some demographics of the general population (e.g. elderly) and the potential for confusion, and space implications on packaging, with the 2D matrix code on the outer packaging for verification of the authenticity of medicines in the supply chain required as part of the falsified medicines directive (Directive 2011/62/EU).

In spite of these limitations, if the PPP materials are available via a common website then the use of a QR code to link to the PPP materials is supported by the PRAC. To overcome the issues related to the 2D matrix code the package leaflet is considered to be the most appropriate place for the QR code to be included. The URL of the corresponding website should also be included for patients without the means to scan a QR code.

Visual reminder (boxed warning/pictogram/symbol)

A warning on the outer box (boxed warning) may be more easily understood than a symbol/pictogram alone. The use of boxed warnings in the SmPC, PL and the outer packaging is therefore recommended to guarantee the reinforcement of important messages regarding the teratogenic effects associated with the use of acitretin, alitretinoin and isotretinoin; the need to use effective contraception, and the strict contraindication in pregnancy (please refer to Attachment 1, *Amendments to the product information as recommended by the PRAC*).

The matter of including a symbol/pictogram on the packaging of medicines known to be teratogenic is one that has generated a wealth of debate across multiple regulatory procedures.

There are several points in favour of the use of a pictogram in relation to the risk of teratogenicity:

- highlighting the risk to all patients, even before reading the PL;
- reminding the HCP about the need to inform that the product is teratogenic; and
- may encourage the patient to look for additional information about the risk, including through questions to relevant HCPs.

In the context of this referral, the usefulness of a striking and visual reminder of the risk was acknowledged during the stakeholder meeting.

However, the use of a pictogram also carries the risk of misinterpretation and that the intended message may not be adequately conveyed. In relation to the message regarding the teratogenic risk, the PRAC agrees that a pictogram alone cannot convey all the necessary information, such as the use of effective contraception and the need to avoid use during pregnancy. To guarantee a full understanding of the potential chosen pictogram/symbol, it would be important to accompany it with a brief explanatory text.

From a regulatory standpoint it is important to ensure that any pictogram is appropriately understood and has been subject to user testing.

In view of the available evidence from studies conducted specifically to test pregnancy warnings on medication packaging, the PRAC recommends that the validated boxed warning text may be accompanied by a symbol for the visual reminder and this should be included on the outer packaging for oral retinoids (acitretin, alitretinoin and isotretinoin).

The decision to implement a symbol/pictogram on the outer package in addition to the minimum visual text reminder (as above), and its graphic content should be taken at national level, considering cultural differences and national preferences on the implementation of symbol /pictogram and input from local patient representatives.

Studies to measure the effectiveness of risk minimisation measures

Regarding the monitoring of the effectiveness of these risk minimisation measures, and recognising the limitations with regards to the data recorded in healthcare databases, a drug utilisation study component (DUS) and a complementary survey study component are recommended (see section 5, *Conditions to the marketing authorisations*).

The study design should aim to evaluate and quantify the effectiveness of the RMM, and should include a pre- and post-implementation analysis and assessment. The MAHs are highly encouraged to collaborate in conducting this study. The protocols should be submitted for assessment by the PRAC within 3 months after Commission Decision. The results of the survey and of the DUS should be submitted within 48 months from Commission Decision. The MAHs are highly encouraged to collaborate in conducting this study conducted according to an agreed protocol

In accordance with the Article 23 of the Regulation (EC) No 726/2004, the products should therefore be included in the list of products for additional monitoring. The black symbol with the corresponding explanatory statement should be included in the product information of the products.

2.4.2. Teratogenic effects – topical retinoids

During the procedure data to evaluate the systemic absorption of topical retinoids was assessed. This evaluation considered the available data in relation to impact of the extent and severity of skin disease, and the physiological changes associated with human pregnancy and in particular changes in skin blood flow.

Based on the limited data available the PRAC concluded that the systemic absorption of topical retinoids is negligible and this is not 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 this 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 of systemic absorption and also the possible risks, 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 it is important that pregnancy is excluded before prescribing.

Considering the above, the PRAC considered that the balance of benefits and risks of topical retinoids in pregnancy is not favourable, and therefore recommended that use of topical retinoids should be contraindicated during pregnancy and in women planning a pregnancy. The SmPC and package leaflet should be updated accordingly (see Attachment 1) to ensure the available data and the risks associated with the teratogenic risk are accurately and consistently addressed within the product information.

The wording proposed by the PRAC should be added or replaced as appropriate. Repeated information in other sections should be deleted. Where more extensive information already exists in the SmPC or package leaflet, it is considered that this should be retained unless it is more restrictive or contradicts the proposed wording by PRAC – in these cases that wording should be deleted. For clarification purposes, recommending the use of effective contraception to prevent pregnancy is considered more restrictive.

2.4.3. Neuropsychiatric disorders - oral retinoids

Severe skin disorders (acne, psoriasis, chronic eczema, skin neoplasms) are known to be associated with an increased risk of psychiatric disorders, and may have a major impact on patients' psychological state, social relationships and everyday activities.

Regarding the oral products, in some studies the authors claim that data arising from pre-clinical, clinical and epidemiological data as well as data from literature reports and spontaneous reporting have failed to confirm the initial signal of a possible causal relationship between isotretinoin and

psychiatric morbidity (Kaymak, Y., et al. (2009)). The authors also mention that these types of adverse events are reported rarely in patients receiving retinoids and there have been no consistent patterns identified, except that psychiatric disorders were mainly reported in the 13-24 year-old age group, which overlaps with the age of the patients receiving retinoids for acne. Moreover, recent studies concluded that successful treatment with oral isotretinoin was associated with an alleviation of depressive symptoms (Kaymak, Y., et al. (2009), Yesilova, Y., et al. (2012), Hahm, B. J., et al. (2009)).

Given the nature of the psychiatric disorder, which may lead also to suicide, the negative impact on patient quality of life may be very high.

Psychiatric disorders are very rarely reported [Research Report B-168'641, Drug Safety Issue Work-up 1998]. Depression is a rarely reported side effect, while psychotic symptoms, suicide attempt and suicide are very rare.

It is recognized that the available data have a number of important limitations that preclude the establishment of a clear causal association (many spontaneous cases confounded by concomitant medication and/or previous medical history of psychiatric disorders and epidemiological studies not able to rule out confounding by indication). Nevertheless, the PRAC considered that the data from patients presented in case series and spontaneous case reports and the individual patients experience are considered to be very important. Taking into account the target patient population and the possible underlying risk of psychiatric disorders, it is advisable that patients taking oral retinoids be warned about the potential risk of psychiatric reactions and the signs and symptoms to look out for. The PRAC therefore agreed that all oral retinoids should contain a warning about the potential risk of neuropsychiatric disorders. Furthermore, particular care needs to be taken in patients with a history of depression and all patients should be monitored for signs of depression and referred for appropriate treatment as necessary.

The current SmPC and PL for some products already contain information that reflects the reported cases. However, based on the data provided by the MAHs provided during this referral or previous PSURs and other concerns raised by third party intervention, it was recognized that the available information on the risk of psychiatric effects is not consistent across the entire class of oral retinoids. In view of this situation the PRAC agreed that a core warning is necessary across all oral retinoids. In addition it should be noted that psychotic symptoms and very rarely, suicidal ideation, suicide attempts and suicide have been reported for patients treated with isotretinoin and alitretinoin but not for acitretin, bexarotene or tretinoin.

The available data therefore support that for the oral retinoids acitretin, bexarotene and tretinoin there be a warning in section 4.4 about the risk of neuropsychiatric disorders. For isotretinoin and alitretinoin the available data support that 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 PI for all products containing systemic retinoids should be updated according to the wording in Attachment 1.

2.4.4. Neuropsychiatric disorders - topical retinoids

Severe skin disorders (acne, psoriasis, chronic eczema, skin neoplasms) are known to be associated with an increased risk of psychiatric disorders and these may have a major impact on patients' psychological state, social relationships and everyday activities. Physiological or pharmacological considerations fundamentally do not support systemic effects, such as neuropsychiatric disorders, of topical retinoids. The total dose of topically administered retinoid is far below the one achieved through

food supplements containing its physiological precursor, namely vitamin A. Such products do not carry any warning on neuropsychiatric effects, as their safety is commonly regarded as established.

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.

2.5. Stakeholders input and other data

2.5.1. Eudravigilance analysis

An Eudravigilance analysis was conducted to support the assessment on the neuropsychiatric disorders for the seven active substances included in this review (single or multi-ingredient formulations). A total of 10,295 case reports of acitretin, adapalene, alitretinoin, bexarotene, isotretinoin, tazarotene and tretinoin-containing medicinal products and any reaction in the Psychiatric SOC in EV was reported up to 19 July 2016.

Oral route of administration was the most frequently reported route of administration. Case reports tend to refer more frequently to patients of male gender. In all age groups, up until the 30-34 age groups, there are more reports of male patients (the difference is greater between ages 15-29). This trend inverts from the age of 35, and from then onwards female gender is always more reported, apart from the age group 75-79 which has the same counts for both genders.

During 2010 and 2012, there was a large increase in the count of case reports with the largest peak in 2011 which correlates with a substantive increase in the case report from non-healthcare professionals. From 2013 onwards the reporting returned to levels similar to those of 1998-2009.

Overall, the nature of the EV data and trends in reporting are in-line with what is already known for the products of concern.

2.5.2. Meeting with patients and healthcare professionals

A meeting with stakeholders was organised as part of the review in order to enhance interaction and exchange of information with a focus on understanding the patients' and HCPs' perspective on the communication, awareness and understanding of the risks of retinoids during pregnancy and in women of childbearing potential and to explore their views on options for improving risk communication. A list of questions to be addressed by HCPs and patient representatives was adopted by the PRAC and a meeting with a broad representation of stakeholders was organised on 3 March 2017.

The main feedback from the meeting is summarised below:

- PPP format is outdated. Messages could be clearer and simpler. Educational materials should be reduced and merged;
- Use of technological advancements in communications is lacking;
- Message should be stronger regarding the severity of risk and options if pregnancies do occur e.g. using images showing malformation and/or a pictogram recognised across the EU to identify medicines with a teratogenic risk;
- Further strengthening the conditions of the PPP in itself would not lead to enhanced compliance;
- Inconsistencies between PPPs were highlighted but also the need to differentiate where needed (e.g. oral vs topical; isotretinoin vs acitretin with regards to duration of teratogenic risk);

- Management of patients' needs strong multi-disciplinary collaboration to enhance compliance;
- Understanding why and which patients fail to follow PPP will also enhance compliance;
- Constant reinforcement of messages is critical (currently lacking with paper-based PPP) – use outer packaging, patient cards and digital tech;
- On-line pharmacy highlighted as risk - retinoids are obtained online without a prescription and where PPP information is lacking;
- It should be reminded to young male patients not to share pills, which can lead to pregnancy.

The same stakeholders were further consulted in writing during the last round of the assessment to provide their views on the clarity of the message in the educational materials, and the details surrounding the content and distribution logistics of the Patient Reminder Card.

3. Benefit-risk balance

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 shows 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 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 the 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 measure (RMM) for these products regarding teratogenic effects, such as strengthening the product information (PI) and additional risk minimisation measure (aRMM) 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 of 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.

4. Risk management

4.1. Pharmacovigilance activity

4.1.1. Non-interventional studies

The PRAC agreed that the MAHs for the oral retinoids acitretin, alitretinoin and isotretinoin should provide revised proposals, including study synopses, for studies to monitor the effectiveness of the risk minimisation measures particularly with regards to patient and prescriber awareness and adherence to the PPP and its risk minimisation measures.

This should comprise a post-authorisation drug utilisation study (imposed as a condition to the MA, category 1). This component is to understand compliance with appropriate drug use and the impact on this. The study design should aim to evaluate and quantify the effectiveness of the RMM, and should include a pre- and post-implemented analysis and assessment.

In addition, the PRAC also requested to conduct a post-authorisation survey study (requested as category 3) to provide complementary information on the prescriber and patient awareness of the PPP and its risk minimisation measures. The survey should assess patients' and prescribers' awareness and adherence to the pregnancy prevention programme. A survey study could also capture data on the use of non-prescription or non-reimbursed contraceptive use which would not be recorded in healthcare databases as part of the DUS.

The results of the survey and of the DUS should be submitted within 48 months from EC Decision. Joint studies to be conducted by all concerned MAHs are strongly encouraged.

4.2. Risk minimisation activities

4.2.1. Amendments to the product information

The PRAC considered that routine risk minimisation measures in the form of updates to the product information would be necessary in order to minimise the teratogenic risk associated with the use of oral and topical retinoid-containing medicinal products, and the neuropsychiatric risk associated with the risk of oral retinoid-containing medicinal products. The changes to sections 4.3, 4.4, 4.6 and 4.8 of the SmPC in relation to the different retinoids are as summarised below:

4.2.1.1. Teratogenic risk associated with the use of retinoids

The PRAC considered that:

- the warnings and precautions of use for the oral retinoids acitretin, alitretinoin and isotretinoin should be revised and other important information harmonised to reflect the teratogenic risk associated with their use;
- A boxed warning for the outer packaging of the oral retinoids acitretin, alitretinoin and isotretinoin should be included with the following key messages:
  - CAN SERIOUSLY HARM AN UNBORN BABY
  - Women must use effective contraception
  - Do not use if you are pregnant or think you may be pregnant
- the use of topical retinoids should be contraindicated in pregnancy and in women planning a pregnancy and the section on fertility, pregnancy and breastfeeding amended accordingly.

The Package Leaflet was amended accordingly.

4.2.1.2. Neuropsychiatric risks associated with the use retinoids

The PRAC considered:

- the warnings and precautions of use for all oral retinoids should be revised and information included to reflect the possible neuropsychiatric risk associated with the use of retinoids ,
- the following adverse reaction(s) should be added under the SOC Psychiatric disorders of the oral retinoids alitretinoin and isotretinoin with a frequency:
  - *Rare*: Depression, depression aggravated, aggressive tendencies, anxiety, mood alteration.
  - *Very rare*: Suicide, suicide attempt, suicidal ideation, psychotic disorder, abnormal behaviour

The Package Leaflet was amended accordingly.

The overall changes to the product information of oral and topical retinoid-containing medicines are summarised in the following table:

	Teratogenic risk			Neuropsychiatric risk	
Oral retinoids					
SmPC section	**4.3****	**4.4**	**4.6**	**4.4***	**4.8**
Acitretin		X		X	
Alitretinoin		X		X*	X
Isotretinoin		X		X*	X
Bexarotene				X	
Tretinoin				X	
Topical retinoids					
SmPC section	**4.3**	**4.4**	**4.6**	**4.4***	**4.8**

	Teratogenic risk		Neuropsychiatric risk		
All topical retinoids	X		X		

* Differentiated wording for alitretinoin, isotretinoin vs. acitretin, bexarotene and tretinoin.

** Oral retinoids already contain appropriate contraindications.

4.2.2. Pregnancy prevention programme

The PRAC recommended that the use of the oral retinoids acitretin, alitretinoin, isotretinoin in WCBP should be subject to stringent restrictions to prevent exposure during pregnancy in view of the teratogenicity due to retinoids. In order to achieve this, the PRAC agreed that an educational pregnancy prevention programme (PPP) should be in place for oral retinoids acitretin, alitretinoin and isotretinoin.

The PPP is aimed at:

- Increasing awareness about the teratogenicity risk during treatment with oral retinoids containing acitretin, alitretinoin and isotretinoin and providing guidance on how to manage that risk;
- Ensuring that the patient is informed about contraception, and has a full understanding of the 'risk period', and what measures need to be observed through this risk period;
- Informing the patient about pregnancy testing requirements, to ensure they understand why it is important, and why 30-day prescriptions ideally are required.

The PPP will include the following conditions:

Individual patient and prescriber discussion should take place to guarantee patient engagement, discuss therapeutic options and ensure the patient understanding of the risks and the measures needed to minimise the risks.

The hazards and necessary precautions associated with retinoids use during pregnancy are presented in the risk acknowledgement form and the patient reminder card which should be provided to the patients.

The prescribers must ensure that the patient has understood and acknowledged the risks of congenital malformations including the magnitude of these risks for children exposed to a retinoid in utero.

Pregnancy testing should be performed prior to initiation of treatment, ideally monthly during treatment and after stopping treatment For alitretinoin and isotretinoin pregnancy testing needs to be performed one month after stopping treatment. For acitretin, women should undergo pregnancy test periodically with 1-3 monthly intervals for a period of 3 years after stopping treatment. The patient should be capable of complying with an effective contraceptive treatment/method, without interruption during the entire duration of treatment with oral retinoids acitretin, alitretinoin, isotretinoin and for 1 month [3 years for acitretin] after the end of treatment

These patients must be provided with comprehensive information on pregnancy prevention programme measures and should be referred for contraceptive advice if they are not using effective contraception. At least one effective method of contraception (preferably a user independent form such as an intra-uterine device or implant) or two complementary forms of contraception including a barrier method should be used. Individual circumstances should be evaluated in each case, when choosing the contraception method involving the patient in the discussion, to guarantee her engagement and

compliance with the chosen measures. In case of amenorrhea, the women should also be on effective contraception.

In case of pregnancy while using the oral retinoids acitretin, alitretinoin, isotretinoin, the treatment must be stopped and the patient be immediately referred to a physician specialized or experienced in teratology for evaluation and advice.

Guidance and details on the conditions of the pregnancy prevention programme are reflected accordingly in the product information and in the updated educational materials (Physician's checklist, pharmacist's checklist and patient reminder card) described in this report.

4.2.3. Educational materials

Prior to the use of oral retinoids containing acitretin, alitretinoin and isotretinoin, the Marketing Authorisation Holder (MAH) must agree the content and format of the educational pregnancy prevention programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The MAH shall ensure that in each Member State where <PRODUCT NAME> is marketed, all healthcare professionals and patients who are expected to prescribe, dispense or use <PRODUCT NAME> have access to/are provided with the following educational package, both available in paper and electronic forms, as applicable:

- **Physician educational material** comprised of:
    - The Summary of Product Characteristics
    - Prescriber checklist/acknowledgement form *(inclusion of patient signature to be agreed at Member State level)*
- **The pharmacist educational material** should contain:
    - The Summary of Product Characteristics
    - The pharmacist checklist *(implementation to be agreed at Member State level)*
- **The patient information pack** should contain:
    - The patient information leaflet (PL)
    - The patient reminder card *(dissemination and inclusion of appointment table to be agreed at Member State level)*

The Prescriber checklist / acknowledgement form shall contain the following key messages:

- That the checklist must be completed for all female patients both at initial and follow-up visits and that a copy should be kept with the patient file.
- The need for the prescriber to ascertain whether the patient is a woman of child-bearing potential.
- A specific reference to the fact that <PRODUCT NAME> is contraindicated in pregnancy and that the patient has been informed and understands the teratogenic risks of <PRODUCT NAME>, e.g. central nervous system abnormalities, facial dysmorphia, cleft palate, external ear abnormalities, eye abnormalities, cardiovascular abnormalities, thymus gland abnormality, parathyroid gland abnormalities, increased risk of abortion, etc.

- The need to provide information on contraceptive choices to the patient, or to refer the patient to a gynaecologist or other suitable HCP if appropriate.
- Information on the fact that contraception is also required for <one month> <three years> after treatment with <PRODUCT NAME>, has stopped.
- That the patient should stop the treatment and rapidly contact their prescriber or other health professional in case she suspects she may be pregnant.
- The need to perform a pregnancy test prior to initiating treatment, and periodically thereafter for the duration of the treatment and one month after stopping treatment <3 years for acitretin> and that the first test should be supervised.
- To inform the patient that the product must not be shared with others.

The pharmacist checklist shall contain the following key messages:

- A specific reference to the fact that <PRODUCT NAME> is contraindicated in pregnancy.
- To inform the patient that <PRODUCT NAME> must not be shared with others and to return any unused product to the pharmacist.
- The prescription of <PRODUCT NAME> is ideally limited to a maximum of 30 days' supply

The patient reminder card shall contain the following key messages:

- That <PRODUCT NAME> is teratogenic and must not be taken during pregnancy.
- That women of child bearing potential should use a highly effective contraception method (i.e. a user-independent form such as an intra-uterine device or implant), or two complementary user-dependent forms of contraception such as oral contraceptive and barrier method.
- The need to perform periodic pregnancy tests for the duration of the treatment and <one month for alitretinoin and isotretinoin> <3 years for acitretin> after stopping treatment.
- To stop the treatment and inform the prescriber as soon as possible in case of suspected pregnancy.
- To inform the patient that <PRODUCT NAME> must not be shared with others and to return any unused product to the pharmacist.

4.2.4. Direct Healthcare Professional Communications/Communication plan

The PRAC agreed that a direct healthcare professional communication (DHPC) should be distributed to inform healthcare professionals of the results of this review and of the changes to the recommendations in the product information of both oral and topical retinoids as well as risk minimisation measures. Accordingly the PRAC agreed the core elements and communication plan of the DHPC. The specialists targeted are general practitioners, dermatologists, gynaecologists, psychiatrists and pharmacists (target group can be further completed/adapted at national level). The timing of distribution will be included in the Communication plan.

4.2.5. Additional channels to improve distribution / receipt of information / educational materials

PRAC agreed that the availability of the educational materials should be available through both printed hard-copy and electronically. Stakeholder (including patients and HCPs) agreed that electronic aids (on-line information, 'apps') can be useful and helpful especially for younger women; however these should be seen as complementary tool and not to replace standards channels of communication.

Electronic distribution of educational materials to HCPs in addition to distribution *via* post is supported by the PRAC. HCPs may have different preferences on how they would like to receive the materials (digital or hard copy).

Pop-up alerts in prescribing and pharmacy dispensing software to remind HCP about the risks of retinoids and the need re-evaluate the use of oral retinoids acitretin, alitretinoin, isotretinoin in WCBP might be an effective strategy to reinforce the implementation of the risk minimisation measures and is supported by the PRAC, the possibilities of which should be explored at national level.

4.2.6. Additional monitoring

In accordance with the Article 23 of Regulation (EC) No 726/2004 the products containing the oral retinoids acitretin, alitretinoin and isotretinoin should be included in the list of products for additional monitoring. The black symbol with the corresponding explanatory statement should be included in the product information of these products.

5. Condition(s) to the marketing authorisations

The marketing authorisation holder(s) for oral retinoids acitretin, alitretinoin and isotretinoin shall complete the below conditions, within the stated timeframe, and competent authorities shall ensure that the following is fulfilled:

A 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 should be implemented in all medicinal products-containing oral retinoids acitretin, alitretinoin and isotretinoin. The details of the visual reminder should be agreed at national level further to a user test taking into account input from local patient representatives.	Within 3 months after Commission Decision
The MAHs of oral retinoids containing acitretin, alitretinoin or isotretinoin shall develop and submit educational materials according to the agreed key elements. These materials should ensure that prescribers are informed and the patients understand and acknowledge the risks associated with oral retinoids acitretin, alitretinoin and isotretinoin in-utero exposure. These should be submitted to the National Competent Authorities:	Within 1 month of Commission Decision.
In order to assess the effectiveness of the updated risk minimisation measures in women of childbearing potential resulting from this referral procedure, MAH(s) of oral retinoids acitretin, alitretinoin and isotretinoin should conduct and submit the results of a drug	

utilisation study (DUS). The study design should aim to evaluate and quantify the effectiveness of the Risk Management Measures, and should include a pre- and post-implemented analysis and assessment. The clinical study report should be submitted to the relevant National Competent Authorities:	Within 48 months after Commission Decision

6. Grounds for 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.

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Divergent position(s)

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

Procedure No: EMEA/H/A-31/1446

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

Retinoids containing medicinal products (INN: Acitretin, Adapalene, Alitretinoin, Bexarotene, Isotretinoin, Tretinoin, Tazarotene)

Divergent statements

Based on the presented pharmacovigilance evidence in their totality, we are of the following opinion:

The undersigned PRAC members agree with most of the conclusions of PRAC reached within this referral procedure, notably with the proposed wording for SmPC and PL for topical retinoids and also with the proposed wording regarding neuropsychiatric disorders for oral retinoids.

The undersigned PRAC members however partially disagree with the recommendation of PRAC regarding the Pregnancy Prevention Programme (PPP) for the oral retinoids acitretin, alitretinoin and isotretinoin:

The article 31 referral was, among others, triggered to evaluate the effectiveness of the PPP taking into consideration that pregnancies did still occur under oral retinoids despite the implementation of the PPP for isotretinoin in 2003 and later on for alitretinoin and acitretin. As a result of the referral a harmonised wording for the product information for all three substances as well as key elements of a tightened Educational Material were proposed, which is in principal endorsed.

However, regular pregnancy tests in women of childbearing potential and a limitation of prescription to a 30 days' supply as well as a 7 days validity of prescription for that patient group were elements of the PPP since 2003. The PRAC now considers that the 7 days validity of prescription cannot be scientifically justified. In addition, monthly pregnancy tests and a limitation of prescription to a 30 days' supply are not considered to be mandatory by PRAC, but are recommended to be followed "ideally" only.

The undersigned PRAC members consider that these elements have been crucial ones of the PPP since 2003. There is no reason to weaken or delete successfully implemented risk minimisation measures now, taking into consideration that pregnancies do still occur under the more stringent regulations so far.

The undersigned PRAC members are also aware of the significant inconsistency with effectively implemented PPPs for other substances with known teratogenicity in humans, i.e. the centrally authorised products containing thalidomide, lenalidomide and pomalidomide. It is the view of the undersigned that such a difference is not scientifically justified and might question the validity of the restrictions in place for these products, may give rise to public concerns in the light of less efforts in pregnancy prevention for retinoids as planned while lacking sufficient justification, or might even mislead to the assumption that retinoids may be considered much safer regarding there teratogenic potential than in the past.

The main objective of the PPP is to protect the unborn child from potential harm caused by highly teratogenic substances. Considering the fact that isotretinoin, alitretinoin and acitretin are indicated to treat non-life-threatening dermatological diseases (such as acne and hand eczema) and that therapy

can be stopped at any time without serious/potentially life-threatening consequences for the patient, the teratogenic risk of these substances might be crucial for the benefit-risk balance if not adequately handled. In this context a pregnancy must certainly be excluded at regular (monthly!) intervals before prescribing (again) an oral retinoid to treat a non-life-threatening dermatological disease. The undersigned PRAC members therefore consider that monthly pregnancy tests and limited prescription for a 30 days' supply in women of childbearing potential as well as a 7 days validity of prescription are stringent but crucial requirements for the use of oral retinoids in women of childbearing potential to ensure close monitoring aiming at maximal protection of the unborn.

In conclusion, it is considered that the changes of the product information and the PPP recommended by PRAC for medicinal products containing acitretin, alitretinoin or isotretinoin for oral use is currently not sufficiently risk proportionate and may negatively impact the safe use of these highly teratogenic substances in women of childbearing potential

PRAC Members expressing this divergent opinion:

- Martin Huber (DE)
- Brigitte Keller-Stanislawski (Independent scientific expert nominated by the European Commission)

The undersigned PRAC member agrees with most of the conclusions of PRAC reached within this referral procedure, notably with the proposed wording for SmPC and PIL for topical retinoids and also with the proposed wording regarding neuropsychiatric disorders for oral retinoids.

The undersigned PRAC member however partially disagrees with the recommendation of PRAC regarding the Pregnancy Prevention Programme (PPP) for the oral retinoids acitretin, alitretinoin and isotretinoin:

The article 31 referral was, among others, triggered to evaluate the effectiveness of the PPP taking into consideration that pregnancies did still occur under oral retinoids despite the implementation of the PPP for isotretinoin in 2003 and later on for alitretinoin and acitretin. As a result of the referral a harmonised wording for the product information for all three substances as well as key elements of a tightened Educational Material were proposed, which is in principal endorsed.

However, regular pregnancy tests in women of childbearing potential and a limitation of prescription to a 30 days' supply as well as a 7 days validity of prescription for that patient group were elements of the PPP since 2003. The PRAC now considers that the 7 days validity of prescription cannot be scientifically justified. In addition, monthly pregnancy tests and a limitation of prescription to a 30 days' supply are not considered to be mandatory by PRAC, but are recommended to be followed "ideally" only.

The undersigned PRAC member considers that these elements have been crucial ones of the PPP since 2003. There is no reason to weaken or delete successfully implemented risk minimisation measures now, taking into consideration that pregnancies do still occur under the more stringent regulations so far. The undersigned PRAC member is also aware of the significant inconsistency with effectively implemented PPPs for other substances with known teratogenicity in humans, i.e. the centrally authorised products containing thalidomide, lenalidomide and pomalidomide. It is the view of the undersigned that such a difference is not scientifically justified and might question the validity of the restrictions in place for these products, may give rise to public concerns in the light of less efforts in pregnancy prevention for retinoids as planned while lacking sufficient justification, or might even mislead to the assumption that retinoids may be considered much safer regarding there teratogenic potential than in the past.

The main objective of the PPP is to protect the unborn child from potential harm caused by highly teratogenic substances. Considering the fact that isotretinoin, alitretinoin and acitretin are indicated to treat non-life-threatening dermatological diseases (such as acne and hand eczema) and that therapy can be stopped at any time without serious/potentially life-threatening consequences for the patient, the teratogenic risk of these substances might be crucial for the benefit-risk balance if not adequately handled. In this context a pregnancy must certainly be excluded at regular (monthly!) intervals before prescribing (again) an oral retinoid to treat a non-life-threatening dermatological disease. The undersigned PRAC member therefore considers that monthly pregnancy tests and limited prescription for a 30 days' supply in women of childbearing potential as well as a 7 days validity of prescription are stringent but crucial requirements for the use of oral retinoids in women of childbearing potential to ensure close monitoring aiming at maximal protection of the unborn.

In conclusion the Mandatory specific prescription form, the 7 day prescription validity, and prescription restrictions for 4 weeks treatment (to facilitate that regular pregnancy testing and monitoring is performed to ensure that the patient is not pregnant before receiving the next cycle of medication) is successfully implemented in the national regulation of Latvia for products with PPP that contain active substances with high risk of teratogenicity (oral retinoids, thalidomide, lenalidomide, pomalidomide). That is in accordance with conditions set by EC to ensure consistent and clear approach regarding the

tools alerting HCP on serious risk and ensuring that defined responsibilities in the controlled distribution programme are fulfilled.

The undersigned PRAC member considers that the provided scientific and regulatory grounds for the deleting of 7 day prescription validity for oral retinoids from the product information and introducing the term “ideally” in the statement that “prescription should ideally be limited to 30 days” within this referral procedure are not sufficiently robust. Thus the mentioned changes are not supported taking into account that they may lead to the weakening of PPP.

PRAC Member expressing this divergent opinion:

- Zane Neikena (LV)