NOTIFICATION TO THE PRAC/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC

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This notification is a referral under Article 31 of Directive 2001/83/EC to the PRAC made by the United Kingdom:

Product name(s), Strength(s) and Pharmaceutical Form(s)	Acitretin, Adapalene, Alitretinoin, Bexarotene, Isotretinoin, Tazarotene, Tretinoin (all strengths, all pharmaceutical forms)
Therapeutic class	Retinoids
Marketing Authorisation Holder(s)	Various

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, in the context of a Periodic Safety Update Report single assessment (PSUSAs) procedure, 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 was gathered from NCAs through a Non-Urgent Request for Information (NUI). This has confirmed the need to review product information and risk minimisation measures across the retinoid class. The responses to the NUI 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. This issue continues to be a subject of public concern. New evidence has been evaluated as it has become available, but although 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 considers that it is in the interest of the Union to refer the matter to the Pharmacovigilance Risk Assessment Committee, and requests 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. As the request results from the evaluation of data resulting from pharmacovigilance activities, the opinion should be adopted by the Committee for Medicinal Products for Human Use on the basis of a recommendation of the Pharmacovigilance Risk Assessment Committee.

Signed: [redacted] Date: 7 July 2016