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 CHMP members agree with most of the conclusions of CHMP 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 CHMP members however partially disagree with the recommendation of CHMP 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 day supply as well as a 7 days validity of prescription for that patient group were elements of the PPP since 2003. The CHMP now considers that the 7 day validity of prescription cannot be scientifically justified. In addition, monthly pregnancy tests and a limitation of prescription to a 30 day supply are not considered to be mandatory by CHMP, but are recommended to be followed “ideally” only.

The undersigned CHMP 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 CHMP 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 their 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 CHMP members therefore consider that monthly pregnancy tests and limited prescription for a 30 day supply in women of childbearing potential as well as a 7 day 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 CHMP 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

CHMP Member expressing this divergent opinion:

- Harald.Enzmann (DE)
- Jan Mueller-Berghaus (Co-opted CHMP member)