

Basilea comments on the Evaluation report for alitretinoin in chronic hand eczema

Throughout the evaluation report there is undue statement of opinion regarding the rate of discontinuation of therapy in the BAP00089 trial without discussion of the relevance of overall discontinuation rates in clinical trials as compared to clinical practice

The rate of discontinuation from the alitretinoin 30mg group of the BAP00089 study is variously described as “high” “very high” and “noteworthy”

- Firstly, we would expect the figure of 25.5% referred to on several occasions to be placed in context. This rate represents the rate of discontinuation for all reasons, including safety, efficacy and administrative reasons
- The all-cause discontinuation rate is comparable to the figures commonly reported in blinded clinical trials of new agents conducted to the standard required by regulatory authorities and as such is not particularly noteworthy
- The rate of discontinuation from trials such as BAP00089 reflects the need for patients to adhere to trial protocol requirements in order to be evaluable according to a stringent analysis plan for marketing authorisation purposes. This may not accurately reflect the common reasons for discontinuing therapy in clinical practice and we would expect some acknowledgement of this fact
- The term “administrative” that is questioned in the evaluation report implies simply that the reason for discontinuation is neither connected with the safety or efficacy of alitretinoin; for example if patients are unable to attend during protocol specified visit windows or become unable to comply with other aspects of protocol defined study conduct they may not be able to continue taking study medication
- Irrespective of opinion whether 25.5% is high, noteworthy or otherwise, the most relevant figure to assess tolerability in clinical practice is the rate of discontinuation for adverse events. This rate was 9.5% in the 30mg alitretinoin group
- The actual rate of discontinuation from alitretinoin 30mg in clinical practice is likely to be considerably lower than 9.5% because dose reduction to 10mg to manage toxicity (as recommended by the product SPC and as commonly practiced by dermatologists with other retinoids) was not permitted by the BAP00089 study protocol

Whereas discussion of the lack of long term safety data for new products and caution in initial use are appropriate, the emphasis on these issues for a new member of the established and widely used retinoid class appears disproportionate relative to the known risks to patients of current comparator therapy

- The evaluation report may inappropriately create the perception that there are valid safety reasons for both the positioning of alitretinoin 3rd line behind current treatment options and the imposition of additional restrictions on its use in the preliminary guidance contained in the ACD
- Clinical experience of retinoids as stated by BAD, BCDS submissions and invited expert opinion at the appraisal committee meeting supports their tolerability and the predictability of their safety profile. This input also emphasises the ability of clinicians to manage the majority of retinoid toxicity by simple dose adjustment
- If it is to form part of the evidential basis for relative positioning recommendations in the ACD, we would expect the evaluation report to place the well characterised safety profile of retinoids in the context of what is known of the acute and chronic toxicity of comparator treatments, including their associated risk of malignancy
- It would be perverse to imply that the demonstrated rate of adverse events or the rates of withdrawal from treatment in the alitretinoin trial justify the positioning of alitretinoin behind comparator treatments in the treatment pathway. It is also biologically implausible to consider that the potential for undetected side effects on longer term follow up provides any risk :benefit justification for placing a physiological vitamin A derivative behind systemic immunosuppressive agents in the management of CHE

It is erroneously stated that thyroid function monitoring is required during alitretinoin therapy. There is no requirement for such monitoring in the marketing authorisation, reflecting the fact that thyroid abnormalities associated with alitretinoin to date have been confined to mild, reversible and asymptomatic laboratory changes