EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

05 September 2019
EMA/PRAC/484308/2019

PRAC List of questions

To be addressed by the marketing authorisation holder(s) for Picato

Procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data

Picato EMEA/H/A-20/1489/C/2275/1489

Marketing authorisation holder(s): LEO Laboratories Ltd.

INN/active substance: ingenol mebutate

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The marketing authorisation holder (MAH) is requested to address the following questions:

Question 1. Please provide information on the cumulative patient exposure to ingenol mebutate in the different EEA Member States and worldwide. This should include data from ongoing and completed clinical trials, non-interventional studies and post-marketing sources; presented separately.

Question 2. Please provide cumulative reviews of all cases of skin tumours observed in clinical studies with ingenol mebutate (including study LP0041-63). This analysis should provide for each study:

- study number
- a summary of the study design including the number of participants in each arm, the method of randomisation, the ingenol mebutate strength/dosage used (average total dose and dose per unit skin area per patient) and site treated
- length of follow-up and timing of follow-up visits
- demographics/baseline characteristics including risk factors for skin tumours (in general) and for particular type of tumour
- compliance and losses to follow-up
- actinic keratosis (AK) area treated, a measure of the average baseline disease severity, criteria for selection of the treatment area
- time since the first application and time since the last application, for each patient
- concomitant therapy
- methods used to assess and classify detected skin malignancies, indicate whether classification of tumours in each trial was based on initial investigator assessment or was determined following assessment by a central pathology reading centre. For all lesions histopathological findings from the study centre and if available from central pathology reading are requested.
- findings (including statistical analyses) for skin tumours both within and outside the treatment area for the different doses, and the combined ingenol group versus those in the vehicle group or comparator arm
- Kaplan-Meier curves for first appearance of tumour (both within and outside the treatment area), including the number of patients at risk and the numbers censored at each time point
- a discussion as to whether violation of the proportional hazards assumption was detected
- a discussion of interaction by application site and whether these data are supportive of a dose-response relationship

All case narratives should also be provided.

Question 3. Please provide a cumulative review of all cases of skin tumours observed in the post-marketing setting. The following details should be provided and analysed for each case: ingenol mebutate strength, AK area treated, whether skin tumour occurred in the treatment area, the type of tumour, risk factors for skin tumours (in general) and for particular type of tumour, time to onset from the first and from the last application, concomitant therapy and previous therapy. Cumulative review should be accompanied by line-listing of all cases reviewed and CIOMS forms.

Question 4. Please provide cumulative reviews of all cases of skin tumours observed in studies with ingenol disoxate (including study LP0084-1369). The same analysis as in question 2 must be provided.

Question 5. Please provide the grounds for early termination of study LP0084-1369 with ingenol disoxate with a full report of adverse events from this trial.

Question 6. Please provide a critical review of all available evidence, including non-clinical data, in relation to any mechanism by which Picato could lead to rapidly accelerated growth or increased incidence of tumours. This review should include any information arising from the *in vitro* colony formation and migration studies in keratinocytes and squamous cell carcinoma cell lines, and also in immortalised AK cell lines, using ingenol mebutate and appropriate controls.

Question 7. Please provide proposals and justifications for any risk minimisation measures (including changes to the SmPC/PL) which may improve the safe use of Picato and how their effectiveness should be monitored.

Question 8. Provide a critical appraisal of the overall impact of the above data on the benefit-risk balance of ingenol mebutate in its authorised indication.