EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Scientific conclusions and grounds for the variation to the terms of the marketing authorisation(s)

Active substance(s): ingenol mebutate

Procedure No. EMEA/H/C/PSUSA/00010035/201807

Period covered by the PSUR: 1 February 2018 to 31 July 2018

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Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for ingenol mebutate, the scientific conclusions of the CHMP are as follows:

Further post-authorisation safety studies to investigate the risk of skin malignancy with Picato are required, based on concerns arising from several clinical trials, in particular:

- A high incidence of skin tumours was seen in the ingenol mebutate arm of the large treatment area trial LP0105-1020.
- An imbalance in the incidence of treatment area tumours between the ingenol mebutate and imiquimod arms continues to be observed in the ongoing long-term safety study LP0041-63.
- In the four studies of the related ester ingenol disoxate a marked increase in skin tumours was seen at 14 months in the treatment arm. An imbalance in tumour incidence was noted for a number of tumour types including basal cell carcinoma (BCC), Bowen's disease and SCC.

Two studies are therefore imposed:

(1) Post-Authorisation safety study: In order to further investigate the incidence of treatment area skin malignancy, particularly squamous cell carcinoma, the MAH should conduct and submit the results of a randomised, double-blind, trial in patients treated with ingenol mebutate compared with vehicle control, over at least 18 months of follow-up. The study should be based on an agreed protocol. The final study report shall be submitted: 31 December 2024

(2) Non-interventional Post-Authorisation safety study: In order to investigate the rate of skin malignancies (squamous cell carcinoma, Bowen's disease, basal cell carcinoma, keratoacanthoma, malignant melanoma) in patients with actinic keratosis treated with ingenol mebutate, the MAH should conduct and submit the results of a cohort study comparing patients treated with ingenol mebutate with patients exposed to other actinic keratosis treatments. The final study report shall be submitted: 31 December 2020

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for ingenol mebutate the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing ingenol mebutate is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.