NOTIFICATION TO THE PRAC/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 20 OF REGULATION (EC) 726/2004

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This notification is a referral under Article 20 of Regulation (EC) 726/2004 to the Pharmacovigilance Risk Assessment Committee (PRAC) made by the European Commission (EC):

Product name/Procedure name	Picato
Active substance	ingenol mebutate
Pharmaceutical form(s)	All
Strength(s)	All
Route(s) of Administration	All
Marketing Authorisation Holder(s)	LEO Laboratories Ltd.

In November 2012 Picato (ingenol mebutate) was authorised in the EU through the centralised procedure for the cutaneous treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis in adults. Picato 150 micrograms/gram gel is for use on the face and scalp while Picato 500 micrograms/gram gel for use on the trunk and extremities.

The mechanism of action of ingenol mebutate for use in actinic keratosis (AK) remains to be fully characterised. *In vivo* and *in vitro* models have shown a dual mechanism of action: 1) induction of local lesion cell death and 2) promoting an inflammatory response characterised by local production of proinflammatory cytokines and chemokines and infiltration of immunocompetent cells.

The potential for Picato to induce skin tumours was considered during the initial marketing authorisation application evaluation. Specifically the risk of AK progression to squamous cell carcinoma (SCC) was reflected in the risk management plan as an important potential risk. The marketing authorisation holder (MAH) was requested to conduct a phase 4 clinical trial assessing the long term cumulative incidence of SCC after treatment with ingenol mebutate gel, 0.015% or imiquimod cream, 5% (Aldara) for multiple AKs on face and scalp (Trial LP0041-63 completion expected in Q1 2020).

In 2017, further to data from a trial (LP0105-1020) comparing ingenol mebutate 0.06% to placebo, the product information of Picato was updated to reflect an excess of skin tumours (keratoacanthoma (KA)).

In parallel an imbalance in the incidence of SCC between the ingenol mebutate and imiquimod arms was observed in the preliminary results of the ongoing long-term safety study imposed at time of initial marketing authorisation. This has been considered to be potentially due to an anti-SCC effect of imiquimod.

In the PSUR assessment covering the period 1 February 2018 to 31 July 2018, a requested meta-analysis of four studies of the related ester ingenol disoxate found a marked increase in skin tumours in the group on active treatment compared to placebo. An imbalance in tumour incidence was noted for a number of tumour types including basal cell carcinoma (BCC), Bowen's disease and SCC. However, it cannot be excluded at this stage that these differences may be observer bias due to partial unblinding of investigators observing local skin responses in patients on active treatment. The pattern of tumour incidence observed in the ingenol disoxate clinical trials is not fully consistent with that observed in studies in which an imbalance in skin tumour was observed in the ingenol mebutate arm. No similar increased tumour incidence was observed in other Picato studies.

It was therefore difficult to draw firm conclusions from the data available in the PSUR in 2018. However, as there was a reasonable possibility that ingenol esters may be tumour-promoting in some patients, the important potential risk 'AK to SCC progression' was updated to 'New skin tumours in treatment area'. In addition two safety studies were imposed to characterise this risk and provide reassurance on long-term safety:

1. A randomised, double-blind, placebo-controlled trial in patients treated with ingenol mebutate, over at least 18 months of follow-up to further investigate the incidence of treatment area skin malignancy.
2. A cohort non-interventional post-authorisation safety study comparing patients treated with ingenol mebutate with patients exposed to other AK treatments to investigate the rate of skin malignancies.

In 2019, the Committee for Medicinal Products for Human Use (CHMP) Scientific Advice Working Party reviewed the protocol of the above mentioned imposed interventional study (study 1) and considered that a substantially larger study than proposed by the MAH would be required to generate meaningful data regarding the incidence of treatment area skin malignancy. Concerns were raised as to the conduct and finalisation of such a safety study in a reasonable timeframe.

Further, during the reporting period of the latest PSUR (1 August 2018 to 31 January 2019) an additional serious case of SCC was reported.

In view of the above concern regarding the potential risk of new skin tumour in the treatment area and the difficulty to generate appropriate data to address the uncertainty about this risk, PRAC considered that a review of all available data, including from ongoing studies, and its impact on the benefit-risk balance of Picato in the authorised indication should be conducted.

In view of the above, the European Commission (EC) initiates a procedure under Article 20 of Regulation (EC) No 726/2004 and requests the Agency to assess the above concerns and their impact on the benefit-risk balance for the centrally authorised medicinal product Picato (ingenol mebutate).

The EC requests the Agency to give its opinion as soon as possible and at the latest by 31 May 2020 on whether the marketing authorisation for this product 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.

In addition, the EC requests the Agency to give its opinion as soon as possible, as to whether provisional measures are necessary to ensure the safe and effective use of this medicinal product.

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Signed Date 3.9.2019

Olga Solomon

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Health and Food Safety Directorate General