Annex I

Scientific conclusions

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The potential for Picato to induce skin tumours was considered during the initial marketing authorisation application evaluation. In 2017, the product information of Picato was updated to reflect an excess of skin tumours (keratoacanthoma (KA)) with ingenol mebutate 0.06% compared to placebo.

Further, an imbalance in tumour incidence in the treatment area was noted in several studies for a number of skin tumour types including basal cell carcinoma (BCC), Bowen's disease and squamous cell carcinoma (SCC) between the ingenol mebutate or its related ester ingenol disoxate and comparator or placebo arms. Several explanations were proposed for these imbalances and no firm conclusions could be drawn. However, in view of the reasonable possibility that ingenol esters may be tumour-promoting in some patients, a randomised controlled trial (RCT) and a non-interventional safety study were imposed to characterise this risk and provide reassurance on long-term safety. Concerns were then raised as to the conduct and finalisation of such RCT in a reasonable timeframe.

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.

On 03 September 2019 the EC therefore triggered a procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data, and requested the PRAC to assess the impact of the above concerns on the benefit-risk balance of Picato (ingenol mebutate) and to issue a recommendation on whether the relevant marketing authorisation (MA) should be maintained, varied, suspended or revoked. In addition, the EC requested the Agency to give its opinion, as to whether provisional measures were necessary to protect public health.

The current recommendation relates only to provisional measures recommended by the PRAC for ingenol mebutate based on the data available at this time. These provisional measures are without prejudice to the outcome of the ongoing review under Article 20 of Regulation (EC) No 726/2004.

Overall summary of the scientific evaluation by the PRAC

Picato (ingenol mebutate) was authorised in the EU under the centralised procedure in November 2012 for the cutaneous treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis in adults. Picato 150 micrograms/gram gel is used on the face and scalp while Picato 500 micrograms/gram gel is used on the trunk and extremities. The potential for Picato to induce skin tumours was considered during the initial marketing authorisation application evaluation and the conduct of a trial was imposed on the MA to investigate the long-term risk of SCC compared to imiquimod (LP0041-63).

PRAC considered the final safety data of this study as well as a cumulative review of all cases of skin tumours in clinical trials with ingenol mebutate and data on skin tumours from randomised clinical trials with ingenol disoxate and from post-marketing reports. PRAC also considered non-clinical data on mechanisms by which Picato might lead to rapidly accelerated growth or increased incidence of tumours. In addition, efficacy data from a recently published trial was considered in the context of the known efficacy of Picato (Jansen, 2019).

The significant statistical difference in the occurrence of skin malignancy between ingenol mebutate and the active control (imiquimod) observed in the interim results of the LP0041-63 trial, is confirmed in the final results (21 cancers versus 6), which is of major concern. While the MAH suggests this might be explained by an intrinsic efficacy of imiquimod, an alternative possibility is that Picato fails to prevent malignancies either because it promotes skin malignancies, or because despite its moderate action on actinic keratosis this does not lead to the expected goal of preventing the development of

skin malignancies. While a difference was also observed between diclofenac and imiquimod in the LEIDA trial (Gollnick, 2019), the difference was more limited and the time to onset is less suggestive as the difference between the two arms appeared at a later stage, in addition both trials cannot be directly compared.

There was a significant statistical difference in the occurrence of skin tumours between ingenol disoxate and vehicle in a pooled analysis of 14-months trials, with a risk difference of 4.9% (95% CI: 2.5%, 7.3%). This is driven by BCC, Bowen's disease, and SCC. Ingenol disoxate is closely related to ingenol mebutate, and its safety profile is considered relevant to characterise that of Picato. The MAH postulated that the results may be confounded by a tendency to biopsy lesions that reoccur in the subjects treated with ingenol disoxate, because these lesions are perceived as 'treatment resistant', which routinely elicits biopsy. This hypothesis cannot be excluded, however the stimulation of tumour growth by ingenol disoxate could also be an explanation for the observed imbalance.

In 8-week follow-up vehicle-controlled clinical trials with ingenol mebutate, there was no significant difference in the occurrence of skin tumours. However, when considering a larger treatment area there is a significant statistical difference in a pooled analysis of three clinical trials driven by the development of KA in severely sun-damaged patients seen in the LP0105-1020 trial. In long term vehicle-controlled clinical trials no significant difference in the occurrence of skin malignancy was observed, whatever the duration of follow-up or treatment area surface. Acknowledging that skin cancers remain relatively rare events which might be difficult to observe in this context, the clearance of AK lesions known to be pre-cancerous by ingenol mebutate would be expected to reduce the occurrence of skin cancers compared to the vehicle arm. The absence of such effect could also suggest that ingenol mebutate treats some precancerous AK lesions, but also promotes some skin tumours, unless the above-mentioned detection bias would intervene.

Post-marketing surveillance has kept reporting increasing numbers of skin cancers, especially SCC. Cumulatively, 84 skins cancers are reported. The majority of the reported skin malignancies were observed less than 4 months after Picato treatment, especially for SCC. Whilst the patient exposure was not estimated, considering the estimated 2.8 million treatment courses administered, this does not appear superior to known background rates of these conditions.

While no clear mechanism could be identified at present for a tumour promoting effect of ingenol mebutate, protein kinase C (PKC)/down-regulation of PKC expression could not be ruled out.

In this context it is also noted that a recently published study provides further evidence on the level of efficacy of Picato at 3 months (67.3% clearance) and at 12 months (42.9% clearance). A high recurrence rate is observed. PRAC noted that in this study the efficacy of Picato is lower to that of 3 alternative treatments (photodynamic therapy (MAL-PDT), imiquimod and fluorouracil). The authors noted that no unexpected toxic events were reported. While it is acknowledged that the study was likely not powered to evaluate malignancy, based on the incidences reported in the clinical trials in which malignancies have been observed with ingenol, cases of malignancy might have been expected. In addition to photodynamic therapy, imiquimod, fluorouracil and diclofenac, the PRAC noted that in case of isolated lesions cryotherapy, curettage, excisional surgery constitute effective alternative options to ingenol mebutate.

Altogether a detailed analysis was available for 14 of the MAH-sponsored clinical trials and a number of uncertainties remain regarding the effect of possible detection bias, an unmasking effect, the effect of the activity of imiquimod on the finding of LP0041-63, retention time in human skin and a mechanism for a tumour promoting effect of ingenol.

The PRAC noted that on 9 January 2020 the MAH of Picato sent a request to the European Commission to withdraw its marketing authorisation. The MAH stated that this request is based on commercial reasons.

Considering the growing concerns regarding a possible risk of skin tumour in the treatment area associated to Picato, including the final results of study LP0041-63 and noting the recent publication of results further supporting that the efficacy of Picato is not maintained over time, the PRAC recommended as a precaution the provisional suspension of the marketing authorisation while the review continues.

Grounds for PRAC provisional recommendation

Whereas,

- The PRAC considered the procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data, in particular regarding the need for provisional measures in accordance with Article 20(3) of Regulation (EC) No 726/2004 for Picato (ingenol mebutate) and taking into account the grounds set out in Article 116 of Directive 2001/83/EC.
- The PRAC reviewed the information currently available to the Committee, from clinical trials, post-marketing reports and non-clinical studies, on the risk of skin tumour in the treatment area in patients treated with Picato (ingenol mebutate). The PRAC also noted the MAH's request to withdraw the MA.
- The PRAC considered of concern the evidence on skin malignancies from all the available data with ingenol mebutate, including the statistically significant imbalance in skin malignancy with ingenol mebutate compared to imiquimod, observed in the interim results of trial LP0041-63, and confirmed in the final study results.
- The PRAC considered the remaining uncertainties regarding a mechanism for a tumour promoting effect of ingenol.
- The PRAC noted that recent study results further support that the efficacy of Picato is not maintained over time.
- Therefore, given the growing concerns on the serious risk of skin tumour possibly associated with Picato, the PRAC provisionally recommend as a precaution while the review continues that patients should no longer be treated with Picato.

The Committee, as a consequence, considers that the benefit-risk balance of Picato (ingenol mebutate) is not favourable.

Therefore, pursuant to Article 116 of Directive 2001/83/EC, the Committee recommends the provisional suspension of the marketing authorisation for Picato (ingenol mebutate).