Annex

Scientific conclusions

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Ever since the initial marketing authorisation application evaluation of Picato, there have been concerns that it may induce skin tumours. 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 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 authorisations should be maintained, varied, suspended or revoked.

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 (AK) in adults. Left untreated AK may progress to skin malignancies. 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. However, ever since the initial marketing authorisation application evaluation, there have been concerns that Picato may induce skin tumours. At time of the initial marketing authorisation the conduct of a trial was therefore 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 statistically significant imbalance in the occurrence of skin malignancy, especially squamous cell carcinoma (SCC), 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 it does not lead to the expected goal of preventing the development of skin malignancies, despite its moderate action on actinic keratosis. In addition, imiquimod is not indicated for the treatment of SCC, in which its efficacy remains to be demonstrated. While an imbalance was

also observed between diclofenac and imiquimod in the LEIDA trial (Gollnick, 2019), the imbalance 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. In the ingenol mebutate arm of trial LP0041-63, skin malignancies occurred in male patients age around 70, mostly with Fitzpatrick skin type II. No patients had an immunocompromised status.

There was a statistically significant imbalance in the occurrence of skin tumours between ingenol disoxate and vehicle in a pooled analysis of four 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, structurally closely related to ingenol mebutate, is considered to have a similar biological activity to that of 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 in 25 cm^2 treatment areas, there was no significant difference in the occurrence of skin tumours. However, when considering a larger treatment area there is a statistically significant 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. Whilst the detection bias described above cannot be ruled out, the absence of such effect could also suggest that ingenol mebutate treats some precancerous AK lesions, but also promotes some skin tumours.

It was also postulated that the observed imbalance in skin tumours may be linked to pre-existing SCC lesions unmasked once the AK effectively cleared with ingenol mebutate. However, if this mechanism is assumed, an increased number of SCCs would be observed in the ingenol mebutate groups compared to the vehicle groups shortly after treatment, which was not the case. In addition, no 'unmasking' effect was observed with other, more effective, AK treatments. Finally, despite the inherent limitations of combining results from studies with different methodologies, an increase of skin malignancies in the treatment area was observed after 4 months in the ingenol mebutate or ingenol disoxate groups compared to vehicle or comparator groups. Therefore, the PRAC considered that any unmasking effect would not explain the imbalance in occurrence of skin tumours.

Post-marketing surveillance consistently reported 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 patient exposure was not estimated, considering the estimated 2.8 million treatment courses administered, this does not appear superior to known background rates for these conditions. However, data from post-marketing cases is difficult to interpret due to protopathic bias. In addition, it is less likely that events would be reported in association with a treatment that was administered several months ago. Thus, the most reliable information derives from randomised controlled trials.

Overall, no risk factors could be identified from the data available that would allow to discriminate patients into low- or high-risk category for skin tumours specific following ingenol mebutate use.

Based on the chemical structure of ingenol mebutate it cannot be excluded that it may have pro-tumourigenic properties. 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.

The PRAC noted that some uncertainty remains regarding the possible effect of detection bias, of unmasking of SCC, of the activity of imiquimod on the finding of LP0041-63, regarding the retention time in human skin and the mechanism for a tumour promoting effect of ingenol. However, as explained above, none of these possible effects would suffice to explain the observed imbalance in skin tumours.

The PRAC also evaluated if measures would allow to minimise the risk to an acceptable level. However, based on the data available, the PRAC could not identify such measures or a patient population in which the balance of benefits and risks would be more favourable.

Taking into account the serious concerns regarding a risk of skin tumour in the treatment area associated to Picato, including the final results of study LP0041-63, that no appropriate risk minimisation measures could be identified and noting the recent publication of results further supporting that the efficacy of Picato is not maintained over time, the PRAC considered the benefit-risk balance of Picato unfavourable in its authorised indication.

The PRAC noted the challenges expressed by the scientific advice working party when reviewing a randomised controlled trial protocol proposed by the MAH to further explore the risk of skin malignancy and question whether it would be feasible owing to the very large sample size that would be needed. The PRAC considered that due to the inherent limitations to the design, non-randomised studies would not provide meaningful data on the concerns at stake.

Grounds for PRAC recommendation

Whereas

- The PRAC considered the procedure under Article 20 of Regulation (EC) No 726/2004, resulting from pharmacovigilance data, for Picato (ingenol mebutate).
- The PRAC reviewed all the information available, from clinical trials, post-marketing reports and non-clinical studies, on the risk of skin tumours in the treatment area in patients treated with Picato (ingenol mebutate).
- The PRAC considered that the evidence on the risk of skin malignancies with ingenol mebutate from all the available data, including the statistically significant imbalance in skin malignancies with ingenol mebutate compared to imiquimod confirmed in the final study results of trial LP0041-63, raised serious safety concerns.
- The PRAC also noted study results supporting the previously observed decreasing efficacy of Picato over time.

- The PRAC could not identify measures to minimise the risk of skin tumours in the treatment area to an acceptable level.
- The PRAC could not identify any sub-group of patients in which benefit from treatment with Picato would outweigh its risks.

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

The PRAC noted the Commission Decision C(2020)856 (final) on 11 February 2020 withdrawing the marketing authorisation of Picato at the MAH's request. Taking into account that said marketing authorisation has been withdrawn, no regulatory action on the marketing authorisation is recommended.

CHMP opinion

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

Overall conclusion

The CHMP, as a consequence, considers that the risk-benefit balance of Picato is not favourable.

Taking into account the Commission Decision C(2020)856 (final) on 11 February 2020 withdrawing the marketing authorisation of Picato at the MAH's request, no regulatory action on the marketing authorisation is recommended.