Part VI: Summary of the risk management plan

Summary of risk management plan for ingenol mebutate

This is a summary of the risk management plan (RMP) for Picato® gel. The RMP details important risks of Picato® gel, how these risks can be minimised, and how more information will be obtained about Picato® gel's risks and uncertainties (missing information).

Picato® gel's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Picato® gel should be used.

This summary of the RMP for Picato® gel should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Picato® gel's RMP.

I. The medicine and what it is used for

Picato® gel is authorised for cutaneous treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis in adults (see SmPC for the full indication). It contains ingenol mebutate as the active substance and it is given by topically administration (as a gel in two strengths; 150 mcg/g and 500 mcg/g).

For centrally authorised medicinal product only:
Further information about the evaluation of Picato® gel's benefits can be found in Picato®'s EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/medicines/human/EPAR/picato

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Picato® gel, together with measures to minimise such risks and the proposed studies for learning more about Picato® gel's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size – the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status – the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of Picato® gel, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Picato® gel is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Picato® gel are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential.

Identified risks are concerns for which there is sufficient proof of a link with the use of Picato® gel. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation.

Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	• Local skin responses • Eye disorders
Important potential risks	• New skin tumours in treatment area • Medication error during treatment of multiple locations
Missing information	• Populations that are immunocompromised / Immunosuppressed • Hypersensitivity

II.B Summary of important risks

Important identified risk – Local skin responses (LSR)	
Evidence for linking the risk to the medicine	Data from clinical trials and post-marketing.
Risk factors and risk groups	Information on this topic is limited. Pre-treatment skin conditions, location of treatment, subjects' skin type and skin sensitivity as well as immune system all may play a role in the intensity of the reaction.
Risk minimisation measures	<u>Routine risk minimisation measures</u> In the EU summary of product characteristics (SmPC), descriptions of local skin responses are included in the following sections: • Section 4.4, Special warnings and precautions for use The occurrence and clinical nature of local skin responses is described in a separate heading, 'Local skin response'. In the 'General' subsection, instructions for proper use is described. • Section 4.8, Undesirable effects Relevant introductory text and adverse events in SmPC Table 1. <u>Additional risk minimisation measures</u> None.

Important identified risk – Eye disorders	
Evidence for linking the risk to the medicine	Data from clinical trials and post-marketing.
Risk factors and risk groups	Exposure of ingenol mebutate gel into the eyes could occur by accident. Subjects anticipated to be at highest risk are those treated for AK lesion on face and scalp locations near the eye. The incidence of accidental eye exposure is expected to be very low.
Risk minimisation measures	<u>Routine risk minimisation measures</u> In the EU SmPC, descriptions of eye disorders are included in the following sections: • Section 4.2, Posology and method of administration Detailed instructions for proper use to minimise the risk of accidental transfer of product to other areas than the treatment area. • Section 4.4, Special warnings and precautions for use Guidance and instructions to avoid the risk and how to treat an accidental exposure to the eyes are included under the headings 'Eye exposure' and 'General'. • Section 4.8, Undesirable effects Adverse events in the SmPC Table 1. <u>Additional risk minimisation measures</u> None.

Important potential risk – New skin tumours in treatment area	
Evidence for linking the risk to the medicine	Data from clinical trials and post-marketing.
Risk factors and risk groups	Phototype, skin and eye colour, number of melanocytic nevi, presence of dysplastic nevi, and individual or family history of skin cancer, type and degree of cumulative sun exposure, history of sunburn, and sun protection behaviour are all risk factors for developing skin tumours. Immunocompromised patients, e.g. immunosuppressed organ transplant recipients or HIV positive individuals, constitute a group that is more susceptible to developing skin cancer and also a more aggressive course may be observed in this population.
Risk minimisation measures	Routine risk minimisation measures In the EU SmPC, description of new skin tumours in treatment area is included in the following section: • Section 4.4 Special warnings and precautions for use The sub-heading 'Keratoacanthoma' states that patients are instructed to be vigilant of lesions developing within the treatment area. • Section 5.1, Pharmacodynamic properties In the heading 'Risk of progression to squamous cell carcinoma', a description of the observed incidence of SCC following ingenol mebutate gel treatment after 12 months follow-up is included. Additional risk minimisation measures None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Ongoing clinical trial: LP0041-63, Risk of squamous cell carcinoma (SCC) on skin areas treated with ingenol mebutate gel and imiquimod cream. Clinical trials in planning phase: Studies of long-term safety of Picato® - planning phase See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk – Medication error during treatment of multiple locations	
Evidence for linking the risk to the medicine	Data from clinical trials and post-marketing.
Risk factors and risk groups	No identified risk group.
Risk minimisation measures	<u>Routine risk minimisation measures</u> In the EU SmPC, description of Medication error during treatment of multiple locations is included in the following section: • Section 4.2, Posology and method of administration Patients are instructed to be careful to use the appropriate strength when simultaneous treatment is prescribed on different body locations. <u>Additional risk minimisation measures</u> None.

Missing information – Populations that are immunocompromised / Immunosuppressed	
Risk minimisation measures	<u>Routine risk minimisation measures</u> In the EU SmPC, description of Populations that are immunocompromised / Immunosuppressed is included in the following section: • Section 4.2, Posology and method of administration A statement that there is no clinical experience, and that systemic risks are not expected, is included. <u>Additional risk minimisation measures</u> None.

Missing information – Hypersensitivity	
Risk minimisation measures	Routine risk minimisation measures In the EU SmPC, descriptions of hypersensitivity are included in the following sections: • Section 4.3 Contraindications • Section 4.8 Undesirable effects Adverse events in the SmPC Table 1. Additional risk minimisation measures None.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

The following studies are conditions of the marketing authorisation:

Studies of long-term safety of Picato®

Purpose of the studies: To gain better understanding of the important potential risk 'New skin tumours in treatment area' (including other tumours besides SCC).

II.C.2 Other studies in post-authorisation development plan

Clinical trial LP0041-63, Risk of squamous cell carcinoma on skin areas treated with Ingenol mebutate gel and imiquimod cream

Purpose of the study: To compare the cumulative incidence of SCC after treatment with ingenol mebutate gel and imiquimod cream.

To compare the cumulative incidence of neoplasia and the short-term and 12-month efficacy of ingenol mebutate gel with imiquimod cream.