Part VI: Summary of the risk management plan

Summary of risk management plan for Alacare 8 mg medicated plaster (5-aminolevulinic acid)

This is a summary of the risk management plan (RMP) for Alacare 8 mg medicated plaster (Alacare). The RMP details important risks of Alacare, how these risks can be minimised, and how more information will be obtained about Alacare's risks and uncertainties (missing information).

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

I. The medicine and what it is used for

Alacare is authorised for the treatment of mild to moderate actinic keratoses (AK) lesions on the face and scalp (hairless areas). (see SmPC for the full indication). It contains 5 aminolevulinic acid (as hydrochloride) as the active substance and it is a medicated plaster for cutaneous use.

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

Important risks of Alacare, together with measures to minimise such 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 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 Alacare is not yet available, it is listed under ‘missing information’ below.

II.A List of important risks and missing information

Important risks of Alacare 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 Alacare. 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 potential risks	Severe application site reaction in combination with photosensitising medication or in patients with photodermatoses
Missing information	Off-label use as repetitive treatment for not completely cleared lesions
	Treatment of immunosuppressed patients

II.B Summary of important risks

Important potential risks **Severe application site reaction in combination with photosensitising medication or in patients with photodermatoses**	
Evidence for linking the risk to the medicine	One publication by Ladner et al. describes a strong photosensitivity reaction in a patient receiving both 5-ALA and hypericin[19]. In this case report 5-ALA was administered systemically whereas Alacare is applied only on the skin. In clinical trials it was shown that systemic uptake of 5-ALA after application of Alacare on the skin is very low. However, based on the presented publication, Alacare treatment together with Hypericin was recognised as a safety concern. In addition to this publication the PRAC recommended the inclusion of photosensitising medication (i.e. medication which induces changes in the skin that makes an individual sensitive to light) in general as an important potential risk since concomitant use of such drugs might lead to severe local reactions (PSUSA/00010006/201306). Besides photosensitising medication concerns arose that underlying photodermatoses, which are skin diseases induced, maintained, or exacerbated by UV-light or sun light (as e.g. sunburn, actinic prurigo,

Important potential risks **Severe application site reaction in combination with photosensitising medication or in patients with photodermatoses**	
	porphyria, and lupus erythematodes), may cause an increased risk for severe application site reactions in patients treated with Alacare/PDT. To date, no case pertaining to severe application site reactions in patients with concomitant photosensitising medication or in patients with photodermatoses has been received. Quality of evidence for “severe application site reaction in combination with photosensitising medication” is considered high to moderate, which means that there is still the possibility that further research may change the estimate. For the concern of ”severe application site reaction in patients with photodermatoses” the quality of evidence is evaluated to be low, meaning that further research is likely to change the estimate. In summary, at that time point experience is considered to limited to refute this safety concern and it is considered as important potential risk.
Risk factors and risk groups	<u>Severe application site reaction in combination with photosensitising medication</u> Patients using medicinal products with known phototoxic or photoallergic potential as concomitant medication. Examples are St. John’s wort, griseofulvin, thiazide diuretics, sulfonylureas, phenothiazines, sulphonamides, quinolones and tetracyclines which may enhance the phototoxic reaction to photodynamic therapy. <u>Severe application site reaction in patients with photodermatoses</u> Patients with a history of photodermatoses are considered to be potentially at higher risk to develop severe application site reactions when treated with 5-ALA PDT. This might be due to an increased baseline risk for photoallergic reactions. While electromagnetic radiation is the critical pathogenic factor with primary photodermatoses, secondary heliotropic diseases have another genesis altogether, although they are also induced by sunlight. Secondary photodermatoses are frequently a feature of systemic diseases such as lupus erythematosus, metabolic disorders such as porphyrias, or disorders of DNA repair such as xeroderma pigmentosum. Initially,

Important potential risks **Severe application site reaction in combination with photosensitising medication or in patients with photodermatoses**	
	patchy erythema develops, accompanied by pruritus. Subsequently, distinct lesions develop. The upper chest, upper arms, backs of the hands, thighs, and the sides of the face are the primary localisations.[35]
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.3 (photodermatoses); 4.4 and 4.5 (both regarding photosensiting medication) Package leaflet Section 2. According to SmPC section 4.4, Alacare should only be administered by a nurse or other healthcare professional trained with the use of photodynamic therapies under the supervision of a physician. Additional risk minimisation measures: none

Missing information

Off-label use as repetitive treatment for not completely cleared lesions	
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.1, 4.2, and 4.4 Package leaflet sections 2 and 3 Additional risk minimisation measures: none

Treatment of immunosuppressed patients	
Risk minimisation measures	Routine risk minimisation measures: none Additional risk minimisation measures: none

II.C Post-authorisation development plan

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

There are no studies which are conditions of the marketing authorisation or specific obligation of Alacare.

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

There are no studies required for Alacare.