# Public Assessment Report

# Scientific discussion

# 5-Aminolevulinezuur Regiomedica 8 mg, medicated plaster

# (5-aminolevulinic acid)

# NL/H/2883/001/DC

# Date: 26 March 2015

**This module reflects the scientific discussion for the approval of 5-Aminolevulinezuur Regiomedica 8 mg, medicated plaster. The procedure was finalised on 6 March 2014. For information on changes after this date please refer to the module 'Update'.**

## List of abbreviations

| | |
|---|---|
| 5-ALA | 5-Aminolevulinic Acid |
| AE | Adverse Event |
| AK | Actinic Keratoses |
| ASMF | Active Substance Master File |
| ALT | Alanine Transaminase |
| AST | Aspartate Transaminase |
| AUC | Area Under the Curve |
| BW | Body Weight |
| CHMP | Committee for Medicinal Products for Human Use |
| CMD(h) | Coordination group for Mutual recognition and Decentralised procedure for human medicinal products |
| CMS | Concerned Member State |
| EDMF | European Drug Master File |
| EMA | European Medicines Agency |
| ERA | Environmental Risk Assessment |
| EU | European Union |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practice |
| GMP | Good Manufacturing Practice |
| HPLC | High-performance Liquid Chromatography |
| ICH | International Conference of Harmonisation |
| LDPE | Low-density Polyethylene |
| MAH | Marketing Authorisation Holder |
| MEB | Medicines Evaluation Board of the Netherlands |
| NOAEL | No Observed Adverse Effect Level |
| NOEL | No Observed Effect Level |
| PAR | Public Assessment Report |
| PDT | Photodynamic Treatment |
| Ph.Eur. | European Pharmacopoeia |
| PK | Pharmacokinetics |
| PL | Package Leaflet |
| PPIX | Protoporphyrin IX |
| RH | Relative Humidity |
| RMP | Risk Management Plan |
| SD | Standard Deviation |
| SmPC | Summary of Product Characteristics |
| SWP | Safety Working Party |
| TSE | Transmissible Spongiform Encephalopathy |
| UV | Ultraviolet |

# I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for 5-Aminolevulinezuur Regiomedica 8 mg, medicated plaster from Regiomedica GmbH.

The product is indicated for treatment of mild to moderate actinic keratoses (AK) lesions on the face and scalp (hairless areas).
A comprehensive description of the indications and posology is given in the SmPC.

After topical application of 5-aminolevulinic acid (5-ALA), its metabolite protoporphyrin IX (PPIX) accumulates intracellularly in the treated AK lesion. The intracellular PPIX is a photoactive, fluorescing compound and, upon light activation in the presence of oxygen, singlet oxygen is formed which causes damage to cellular compartments of the light-exposed target cells, in particular the mitochondria.

Currently, there are three registered products containing 5-aminolevulinic acid or its methylester for the indication actinic keratoses: Alacare 8 mg medicated plasters (UK/H/1533/001), Metvix, a cream containing 16% methyl aminolevulinate hydrochloride (SE/H/0266/001) and Ameluz, a gel containing 7.8% 5-aminolevulinic acid as hydrochloride (EU/1/11/740/001).

This decentralised procedure concerns a full application pursuant to Article 8(3) of Directive 2001/83/EC, with a known active substance. As 5-aminolevulinic acid has been used for many years, the dossier is partly supported by literature.

The concerned member states (CMS) involved in this procedure were Belgium, Czech Republic and Slovakia.

The clinical development program consisted of five clinical trials: one pharmacodynamic study (AK01), one pharmacokinetic study (AK05), one dose-response study (AK02) and two efficacy and safety studies (AK03 and AK04).

In all clinical studies, the 5-ALA patch was used once. As the active substance is well known, the clinical development program is considered sufficient.

No regulatory guidance or advice was sought or obtained for the clinical trials. A class waiver (P/345/2010) has been granted according to Article 7 of the Paediatric Regulation 1901/2006, as actinic keratosis does not normally occur in the paediatric population.

# II. QUALITY ASPECTS

## II.1 Introduction

The5-Aminolevulinezuur Regiomedica plaster has a size of 4 $cm^2$, is square with rounded corners and consists of a skin tone backing foil and a self-adhesive matrix, covered by a release liner which is removed prior to use. Each medicated plaster of 4 $cm^2$ contains 8 mg 5-aminolevulinic acid (as hydrochloride), 2 mg per $cm^2$.

The plasters are packed in a protective sachet consisting of 4 layers: paper (outer layer), polyethylene LDPE, aluminium, ethylene copolymer (inner layer). Four medicated plasters are sealed in one sachet.

The excipients are:
Plasters - Acrylic pressure sensitive adhesive
Backing film - Pigmented polyethylene aluminium vapor coated polyester
Release liner (removed prior to application) - polyethylene terephthalate film

## II.2 Drug Substance

The active substance is 5-aminolevulinic acid, an established active substance however not described in the European Pharmacopoeia (Ph.Eur.). It is a white to off-white crystalline powder, which is freely soluble in water and slightly soluble in ethanol and methanol.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
5-Aminolevulinic acid hydrochloride is synthesized in three reaction steps. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance
An appropriate drug substance specification has been established in-house. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three production-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for 7 production-scale batches stored at 5°C (6 months) and -20°C (up to 60 months). No changes were observed. Based on the submitted data the claimed storage condition of -20°C and retest period of 3 years are considered acceptable.

## II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The product was developed by *in vitro* cadaver skin permeation studies. Several batches were developed distinguished by particle size of the drug substance, % drug substance in the adhesive, type of adhesive and thickness of the adhesive matrix layer. Microbial contamination is controlled in the Finished Product Specification according to Ph Eur 5.1.4 Category 2. The adhesive force has been investigated and is acceptable.
All clinical and stability batches were manufactured according to the selected final formulation. No *in vivo*/*in vitro* correlation was made. The dissolution testing was only considered a quality tool to control the release of the drug substance from the medicated plaster in accordance with the Ph.Eur. monograph on semi-solid preparations for cutaneous application.
The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process is separated into four individual steps: preparation of the drug containing adhesive mass, mass coating and laminating processes, laminate slitting, and a single patch punching and pouching process. The manufacturing process has been adequatelyvalidated according to relevant European guidelines. Process validation data on the product has been presented for three production-scale batches.

Control of excipients
The excipients have been adequately described and appropriate specifications have been provided.

Quality control of drug product
Theproduct specification includes tests for appearance, identity, adhesive weight per patch, content of 5-ALA HCl per patch, content uniformity, *in vitro* dissolution, related substances, residual solvents, adhesive force, peel force, pouch tightness and microbiological examination. The release and shelf-life limits are identical with the exception of the dissolution limits. Furthermore, identity and adhesive weight per patch are not included in the shelf-life limits. The release and shelf life limits are acceptable. The analytical methods have been adequately described and validated. Batch analytical data have been provided for 1 laboratory-scale batch, 3 pilot-scale batches and 3 production-scale batches. All batches complied with the specifications.

Stability of drug product

Stability data on the product has been provided for 2 pilot-scale and 1 full-scale batch stored at 25°C/60% RH (36 months) and 30°/65% RH (36 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed packaging.

At accelerated conditions an increase in peel force was observed in all batches. At long-term and intermediate conditions a decrease in *in vitro* release after 0.5 h was observed after 36 months. However, the amount stayed above the specification limit.

For the in-use stability study the pouch was opened and two patches were removed from the protective layer. The opened pouch was put on stability study and stored at 25°C/60% RH (3 months). A slight increase in impurities was observed in both batches. However, the data stayed well within the specification limits. An increase in peel force was observed, which also remained well below the specification limit.

Based on the submitted stability data the proposed shelf-life of 36 months is acceptable. The applicable in-use shelf life is 3 months when stored in the sachet. Since the storage condition in the SmPC is ”After opening, store plaster in the sachet” and the sachet is impermeable to light, no additional photostability study is required.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

### II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that5-Aminolevulinezuur Regiomedica 8 mg, medicated plaster has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

No post-approval commitments were made.

## III. NON-CLINICAL ASPECTS

### III.1 Introduction

The MAH has reviewed the relevant preclinical pharmacology and pharmacodynamic studies in the literature. The pharmacokinetic profile of 5-ALA was described using studies performed by the MAH and literature publications. In addition, toxicity studies were conducted, supported by literature data.

The studies undertaken by the MAH have been performed, in general, according to Good Laboratory Practice (GLP). Not all of the supplementary experiments, submitted as literature reference, have been conducted according to GLP.

### III.2 Pharmacology

The non-clinical pharmacology dossier, which comprises data generated by the MAH and supportive literature references, presents the scientific rationale and justifies the proposed use of 5-ALA in treatment of AK. The MAH has adequately reviewed the relevant pharmacology and pharmacodynamic studies in the literature. The primary pharmacodynamics of 5-ALA have been well-established in studies relevant to the proposed indication.

No secondary pharmacodynamic studies have been conducted and this part of the dossier is based on literature references. The published studies cited provide a satisfactory illustration of the secondary pharmacodynamic profile of 5-ALA. As there is adequate clinical experience in the intended indication with this compound, no further secondary pharmacodynamic studies are necessary.

Safety pharmacology studies show that 5-ALA did not influence the gastrointestinal and central nervous systems. A slight increase in saluresis was seen following intravenous administration of 5-ALA. Cardiovascular and respiratory effects seen in dogs were considered to be linked to i.v. dosing and were reversible. Considering the proposed route of administration (dermal) it is unlikely that these

findings are of any significance.
No drug interaction studies have been performed. The results of pharmacodynamic drug interaction studies described in the literature do not indicate interactions.

### III.3 Pharmacokinetics

The pharmacokinetic profile of 5-ALA was described using studies conducted by the MAH and literature publications.
5-ALA is well absorbed after oral administration. Its absolute bioavailability in dogs is about 86% after administration of 20 mg/kg dose. The pharmacokinetic profile of 5-ALA orally administered to dogs and humans is similar after equivalent doses (20 mg/kg), however differences are seen in systemic PPIX concentrations where PPIX levels were higher in humans than in dogs. No non-clinical absorption data has been provided following topical administration of 5-ALA. However, the provision of clinical data following topical application of 5-ALA negates the need for animal pharmacokinetic data and the lack of pharmacokinetic studies using the intended clinical route of administration is acceptable.
Human pharmacokinetic parameters were assessed after topical application of 8 patches in patients with AK lesions and after oral administration of 20 mg 5-ALA HCl/kg in healthy volunteers. A considerably lower average AUC value (56 – 86 fold) was seen following topical application of 5-ALA, suggesting that limited systemic exposure will be gained via the intended clinical route.
Published studies using the topical administration of 5-ALA HCl in nude mice resulted in systemic availability of 5-ALA in plasma. The increase in 5-ALA levels was dependent on the vehicle, the duration of the application and the concentration of 5-ALA HCl in the vehicle. After topical administration of 5-ALA to tumour bearing mice, blood porphyrin levels are highest at 3 h and then return to baseline levels. Porphyrins also accumulate in liver and spleen. Using nude mice it was shown that after topical administration of 5-ALA, PPIX concentration was highest in the skin, followed by intestine, liver and remote skin. Consequently the excretion of 5-ALA and its metabolites in these mice is also increased. Excretion of 5-ALA occurs mainly through the kidneys. 5-ALA is an endogenous compound which undergoes a well-known biotransformation process in the heme synthesis pathway and does not raise any concerns from metabolic point of view.

### III.4 Toxicology

Single dose toxicity
In the application no acute toxicity studies using the intended route of administration have been conducted or cited from the literature. As 5-ALA is an endogenous substance coupled with the low order of toxicity seen in the acute toxicity studies, reassurance is provided that 5-ALA is unlikely to pose any toxicological concern. The no observed effect level (NOEL) of 5-ALA in acute toxicity studies is several hundred fold above the intended topical administration dose in patients.

Repeated-dose toxicity
The liver was the target organ in 2- and 4-week repeated-dose toxicity studies in rats and dogs following oral (gavage) or i.v. administration of 5-ALA HCl. Increased liver weight, discoloration, bile duct changes and changes in clinical biochemistry were recorded. There was no obvious difference in the findings between sexes. The bile duct changes were not reversible within a 14-day recovery period. In the 4-week study in dogs, AST and/or ALT activity level showed a recovering trend at 4 weeks after cessation of treatment, and the degree of pigmentation seemed to become slightly milder, indicating also a gradual recovery of pigmentation within this time interval.
In the 2-week studies, no observed adverse effect level (NOAEL) values are below 30 mg/kg (rat, oral), 125 mg/kg (rat, intravenous), and 3 mg/kg (dog, intravenous), as adverse effects were observed at the lowest doses tested. In the 4-week toxicity study in dogs (oral administration), there was a NOAEL of 3 mg/kg/day.
Since the systemic exposure to 5-ALA after intended single, topical application of the 5-ALA plaster is considered low as compared to the repeat dose toxicity studies in rat and dog, accumulation of 5-ALA or PPIX after application of the plaster is considered rather unlikely.

Genotoxicity
The *in vitro* and *in vivo* genotoxicity tests performed by the MAH did not reveal significant genotoxic potential of 5-ALA in the absence of light. Possible genotoxic properties of 5-ALA, as described in the literature, seem to be light-dependent, being a consequence of porphyrins formation and their destruction induced by light activation. A local photogenotoxic effect cannot be completely ruled out. Precautionary sunlight protective measures of the treated area for 48 hours are recommended in the

SmPC despite the likelihood that all PPIX will undergo photobleaching during photodynamic treatment (PDT).

Carcinogenicity
The lack of conventional carcinogenicity studies is acceptable when bearing in mind the dosing regimen, lack of mutagenic potential, limited absorption and the patient population. Literature studies have been supplied which provide reassurance that 5-ALA is not likely to be carcinogenic. There is no clinical evidence of higher skin cancer rates in patients with photosensitivity diseases.

Reproduction toxicity
The lack of reproductive toxicity studies on the 5-ALA plaster is considered to be acceptable in view of the limited adsorption, the safety profile following i.v. dosing and the fact that 5-ALA is a naturally occurring cell constituent.
Limited information has been provided on the effect of the active substance on reproduction. An oral study in rabbits on embryo-fetal development determined a NOAEL of 50 mg/kg/day for general toxicity (reduced feed intake and weight loss) in maternal animals and 150 mg/kg/day for maternal reproductive function and embryo-foetal development.
Evidence collected from published studies indicates that 5-ALA exhibits reproductive and developmental toxicity which is strictly related to light activation. There was no evidence of toxicity to reproduction in light-protected conditions. There is also no information of 5-ALA on maternal function and it is not known whether 5-ALA is distributed into milk. There is also no information of 5-ALA on fertility. This is reflected in the SmPC.

Phototoxicity
After application of 5% 5-ALA HCl in cream in rabbits, no 5-ALA induced skin changes were observed and no sensitizing potential was identified using the Magnusson and Kligman test model in guinea pigs. It is noted that these experiments were conducted under dimmed light. Topical 5-ALA treatment and subsequent illumination is known from both preclinical and clinical studies to induce local reactions as the primary pharmacodynamic effect of 5-ALA is the induction of PPIX-mediated phototoxic damage in the treated skin lesions. In patients, it is likely that healthy skin surrounding the AK lesion will be exposed to 5-ALA. While it has been shown that PPIX accumulation is lower in healthy skin than in UV induced lesions, the MAH recommends in the SmPC that the treated skin and surrounding skin area be protected from sunlight exposure during 48 hours after PDT to avoid any additional local phototoxic reactions.

Immunotoxicity
In the repeated-dose toxicity studies, there were no signs of an immunotoxic effect. In addition, there were no non-clinical concerns in relation to skin sensitization. Suppression of the contact hypersensitivity response following topical administration of 5-ALA-PDT to a large area in mice has been described in the literature. There is no clinical evidence of suppression of the hypersensitivity response and in light of clinical experience in immunosuppressed patients the risk seems minimal.

Local tolerance
To determine the safety of the 5-ALA plaster, the MAH has conducted a 4-week local tolerance study in minipigs following repeated epicutaneous application on intact and scarified skin. Each animal was treated with the patch intended for clinical use and a control patch which contained no active substance. No differences in local tolerance reactions, histopathology or macroscopic findings were observed when comparing the test and control patch. It is considered that there are no concerns associated with local tolerance of the proposed product on repeat administration.

Impurities
The impurities associated with the drug substance and drug product are well controlled and within the limits set out in ICH guidelines and in the European Pharmacopeia, therefore no toxicological qualification is necessary.

### III.5 Ecotoxicity/environmental risk assessment (ERA)

An acceptable justification has been provided for the absence of an environmental risk assessment in line with the guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/447/00). The drug substance is an amino acid, which, according to ERA guideline (CHMP/SWP/4447/00), does not require an ERA. Appropriate attention has been paid to the proposed disposal of the patch and associated wordings in the product particulars.

### III.6 Discussion on the non-clinical aspects

The non-clinical dossier includes an appropriate overview on the pharmacology, pharmacokinetics and toxicology, which is based on up-to-date and adequate scientific literature. The MAH conducted relevant additional non-clinical studies.
Since 5-Aminolevulinezuur Regiomedica is a novel formulation with a known active substance and its intended use is the treatment of AK, the expected primary pharmacodynamic effects were tested and confirmed directly in AK patients (in the clinical studies AK01 and AK02). Similarly, a pharmacokinetic study was carried out only in AK patients and no preclinical pharmacokinetic studies with the plaster have been performed. The member states agree that no further non-clinical studies are required.

## IV. CLINICAL ASPECTS

### IV.1 Introduction

5-ALA is an endogenous compound and plays a role as precursor in the biosynthesis of e.g. hemoglobin or cytochrome C1. Intracellularly, 5-ALA is metabolised to protoporphyrin IX (PPIX) which has fluorescent properties when activated by red light (~630 nm). The exogenous application of 5-ALA leads to an accumulation of PPIX in e.g. (pre)malignant lesions.
5-ALA-induced PPIX can be used as a photosensitiser in photodynamic therapy (PDT). After activation with light of the appropriate wavelength, reactive oxygen species (singlet oxygen) are formed. These reactive oxygen species cause damage to cells and tissues, resulting in apoptosis and necrosis. This mechanism is used in PDT for the destruction of malignant and premalignant tissue.

The clinical development program consisted of one pharmacodynamic study (AK01), one dose-response study (AK02) and two efficacy and safety studies (AK03 and AK04). In addition, the pharmacokinetics were investigated (AK05).

All clinical studies were designed, conducted and analysed according to the current research standards of Good Clinical Practice (GCP). All applicable laws, ICH guidelines, guidances and Points to Consider were followed.

**Table 1.** Overview of clinical studies performed with 5-ALA Regiomedica

| Study | Study design | Inclusion criteria | Enrolled subjects | Treatments | Endpoints |
|---|---|---|---|---|---|
| **Supportive studies** | | | | | |
| **AK01**<br>Influence of application duration (2h, 3h, 4h or 5h) of 5-ALA patch on the PPIX fluorescence in AK | Open, single centre, intra-individual comparison. Four lesions and two areas of healthy skin randomized to different application times. | • Caucasian male/female<br>• ≥ 18 years<br>• Clinically manifested diagnosis of AK with at least four locally separated lesions<br>• Skin type I to III according to Fitzpatrick<br>• Mild to moderate lesions (grade I – II)<br>• Distance between lesion borders > 1.5 cm | N 13 | 5-ALA patch | Primary:<br>PPIX fluorescence at 0h after removal of patch<br><br>Secondary:<br>PPIX fluorescence at 2h, 4h, 6h, 24h and 48h after removal of patch<br><br>Decrease in fluorescence after removal of patch over 48h<br><br>Phototoxicity in normal healthy skin after 2 and 5 hours application. |
| **AK02**<br>Determination of the optimal application duration (0.5, 1, 2 or 4 h) | Observer blinded, multicentre, randomized, 4-arm parallel group study | • Caucasian male/female<br>• ≥ 18 years<br>• Diagnosis of AK proven histologically in the patient's history with at least three locally separated lesions<br>• Skin type I to III according to Fitzpatrick<br>• Mild to moderate lesions (grade I – II)<br>• Distance between lesion borders ≥ 1.0 cm<br>• Max diameter of lesion 1.8 cm | N 165 | 5-ALA patch, followed by single PDT* | Primary:<br>Complete clearance rate of treated AK lesions at week 8 after therapy<br><br>Secondary:<br>Safety<br><br>Efficacy at week 4 (lesion basis)<br><br>Efficacy at week 4 and 8 (patient basis) |
| **Main studies** | | | | | |
| **AK03**<br>Comparison of the efficacy of 5-ALA patch-PDT with placebo-PDT for the treatment of mild to moderate AK | Observer and patient blinded, randomized, placebo-controlled, multicentre study | • Caucasian male/female<br>• ≥ 18 years<br>• Diagnosis of AK with at least three locally separated lesions on the head and/or face | N 107 | 5-ALA patch or placebo, followed by single PDT* | Primary:<br>Complete clinical clearance of an AK lesion at week 12.<br><br>Secondary:<br>Safety<br><br>Efficacy at week |

| | | | | | |
|---|---|---|---|---|---|
| 12 after therapy | | • Skin type I to IV according to Fitzpatrick<br>• Mild to moderate lesions (grade I – II)<br>• Distance between lesion borders ≥ 1 cm<br>• Max diameter of lesion 1.8 cm | | | 12 (patient basis)<br><br>Efficacy at 6, 9 and 12 months (lesion and patient basis)<br><br>Cosmetic outcome 12 weeks, 6, 9 and 12 months |
| **AK04**<br>Comparison of the efficacy of 5-ALA patch-PDT with placebo-PDT and cryosurgery for the treatment of mild to moderate AK 12 w after therapy | Open randomised prospective multicentre study | • Caucasian male/female<br>• ≥ 18 years<br>• Diagnosis of AK with at least four locally separated lesions on the head and/or face<br>• Skin type I to IV according to Fitzpatrick<br>• Mild to moderate lesions (grade I – II)<br>• Distance between lesion borders ≥ 1 cm<br>• Max diameter of lesion 1.8 cm | N 349 | 5-ALA patch or placebo, followed by single PDT* or cryosurgery | Primary:<br>As in AK03<br><br>Secondary:<br>As in AK03 |

* Photodynamic treatment, red light, dosage 37 J/cm², wavelength 630 ± 3 nm

### IV.2 Pharmacokinetics

To support the pharmacokinetics of 5-ALA, the following pharmacokinetic studies were submitted.

**Table 2.** Clinical development programme: pharmacokinetic studies.

| Study Code | Study Title | Study Objective |
|---|---|---|
| AK05 | Evaluation of the pharmacokinetics of 5-aminolevulinic acid after topical application of 5-ALA plaster to actinic keratoses | PK of 5-ALA after application of 5-ALA patch to AK lesions.<br>Secondary aims: PK of PPIX, safety and tolerability |
| MCALS.20/BV | Single dose study on the absolute bioavailability of oral doses of 20 mg/kg BW 5-aminolevulinic acid in comparison to 2 mg/kg BW i.v. administration in healthy male subjects | Absolute bioavailability i.v. vs. p.o.<br>Secondary aim: Duration of photosensitisation |
| 086/06-05.ALA | Determination of the protein binding of 5-aminolevulinic acid in human plasma | Validation of a HPLC method for quantitative determination of 5-ALA in water<br>Determination of protein binding of 5-ALA in human plasma using ultrafiltration |

The results of the studies show that after application of eight 5-ALA patches for 4 hours on mild to moderate AK lesions, 5-ALA is absorbed and reaches systemic circulation. The mean maximum peak plasma concentrations of 5-ALA reached approximately 20 µg/L above the baseline concentrations at 4 hours post-dose. 5-ALA levels returned to baseline within 24 hours. No PPIX concentrations above the lower limit of quantification ere observed. The MAH also submitted literature indicating that systemic side effects, like skin phototoxicity, occur at much higher exposure (oral administration of 20-60 mg 5-ALA/kg BW) than what is seen in study AK05. Based on this and on the submitted literature, it can be concluded that there is no risk of general photosensitivity after application of eight patches for 4 hours. Plasma protein binding of 5-ALA is considered to be low. It was independent of the concentration and averaged 12.5%. The excretion of 5-ALA in urine in the first 12 hours after application was low with a maximum of 2.06% of the dose administered and a median of 1.39%.
The MAH did not conduct any interaction studies since systemic exposure is considered low. The risk of decreased efficacy/loss of efficacy when enzymes of heme biosynthesis are inhibited is also considered low. 5-ALA Regiomedica should not be used in patients with porphyrias, in which enzymes of the heme synthesis are partially inhibited. Further, no drugs are identified that would inhibit heme synthesis.

## IV.3 Pharmacodynamics

Study AK01 was performed to evaluate PPIX fluorescence after different application durations of the 5-ALA patch. The study was an open, single centre study with intra-individual comparison. Four lesions and two areas of healthy skin per patient were randomized to different patch application times (2, 3, 4 or 5 hours). The study included 13 patients and lasted for 48 hours. The primary endpoint was fluorescence at 0 h after patch removal. The main data are presented below.

**Table 3.** Patient characteristics and results of supportive clinical study AK01.

| **Patient characteristics** | |
|---|---|
| **N randomized**<br>**N completed** | 13<br>13 |
| **Age, mean (SD)** | 68.8 (9.78) |
| **Sex (% female)** | 16% |
| **N of lesions** | Not reported |
| **Severity of lesions**<br>**mild**<br>**moderate** | <br>73%<br>27% |
| **Results** | |
| **Fluorescence at 0h (mean, SD), AK lesions**<br>**Duration of application (hours)**<br>**2**<br>**3**<br>**4**<br>**5** | <br><br><br><br>1.558 (0.403)<br>2.496 (0.856)<br>3.183 (1.041)<br>3.407 (0.980) |
| **Fluorescence at 0h (mean, SD), healthy skin**<br>**Duration of application (hours)**<br>**2**<br>**5** | <br><br><br><br>0.823 (0.157)<br>1.598 (0.649) |

The study demonstrated fluorescence increases with the duration of the patch application except for the 4h and 5h applications on AK lesions which showed comparable fluorescence levels. Remarkably, fluorescence kept increasing until 6 hours after removal of the patch (fluorescence ranged from 4.191 to 5.072, increasing with application duration) and did not return to baseline before the end of the monitoring period (48 hours after removal of the patches) and were still more than 3 times larger than immediately after removal of the patch. Time points between 6 and 24 hours were not measured. Fluorescence levels were clearly lower for normal skin than for AK lesions.

With a shorter duration of application than the chosen 4 hours, fluorescence levels increase to comparable levels to the 4 hours application duration, but only at 2 to 4 hours after patch removal.
Therefore for convenience reasons, an application duration of 4 hours and illumination right after patch removal is preferable over shorter application durations.

## IV.4 Clinical efficacy

The efficacy of 5-ALA Regiomedica was studied in three clinical studies: AK02, AK03 and AK04, of which the latter two are considered pivotal.

**Supportive study AK02**

The aim of the study was the determination of optimal application duration (2h, 3h, 4h or 5h) of the 5-ALA patch. The primary endpoint of the study was complete clearance rate of treated AK lesions at week 8 after therapy. The table below presents the patient disposition, characteristics and results of study AK02. Two patients discontinued treatment which was sufficiently explained.

**Table 4.** Patient characteristics and results of supportive clinical study AK02.

| **Patient characteristics** | |
|---|---|
| **N randomized**<br>**N completed** | 149<br>147 |
| **Age, mean (SD)** | 70.5 (8.42) |
| **Sex (% female)** | 27% |
| **N of lesions**<br>**3**<br>**4** | <br>28%<br>72% |
| **Severity of lesions**<br>**mild**<br>**moderate** | <br>57%<br>43% |
| **Results** | |
| **Lesion based clearance rate**<br>**Application duration**<br>**0.5h**<br>**1 h**<br>**2h**<br>**4h**<br>**Responder****<br>**Application duration**<br>**0.5h**<br>**1 h**<br>**2h**<br>**4h** | <br><br>54%<br>73%<br>75%<br>86%<br><br><br>27%<br>50%<br>51%<br>74% |

*Note: Based on 146 subjects. Three subjects were not analysed due to mistake in application duration.*
*** Defined as complete clearance of all lesions*

The lesion based results indicate that efficacy increases with longer duration of application. Responder percentage increases and is highest with the 4 h application duration which was chosen for the pivotal studies.
There was no difference in clearance levels between mild and moderate lesions. Females showed a slightly higher clearance rate than men in other treatment groups, except for the 4 hour group. However, the difference was small and could be by chance due to the low number of women included in the study.

Local adverse events during application of the patch did not differ between the 2 and 4 hour duration group, however during illumination, adverse reactions increased in a dose-dependent manner. Five patients in the 4 hour duration group (11%) experienced a severe local reaction, as compared to none in the 2 hour group. After therapy, 17% of patients in the 4 hour group experienced a severe AE as compared to 11% in the 2 hour group.

**Main studies – AK03 and AK04**

Study AK03 compared the 5-ALA patch to placebo and study AK04 to placebo and cryosurgery. Both studies were patient blinded, randomized, multicentre studies, and observer blinded for placebo and 5-ALA patch, but cryosurgery could not be blinded due to different skin reaction between PDT therapy and cryosurgery. The MAH referred to hypopigmentation after cryosurgery, which would unblind the observer. This is considered justified.
In study AK03 randomization allocation ratio was 2:1 (5-ALA Regiomedica vs. placebo) and in study AK04 3:3:1 (5-ALA Regiomedica vs. cryosurgery vs. placebo).

Study AK03 included patients with three to eight lesions while in study AK04 patients were required to have four to eight lesions.

**Table 5.** Patient disposition and characteristics in the main clinical studies AK03 and AK04.

| | **AK03** | | **AK04** | | |
|---|---|---|---|---|---|
| | **placebo** | **5-ALA** | **placebo** | **5-ALA** | **cryosurgery** |
| **Patient characteristics and disposition** | | | | | |
| **N randomized** | 34 | 69 | 49 | 148 | 149 |
| **N completed (until week 12)** | 33 | 66 | 48 | 144 | 139 |
| **Age, mean (SD)** | 71.5 (6.83) | 70.4 (8.46) | 71.4 (8.39) | 69.8 (8.42) | 70.5 (8.42) |
| **Sex (% female)** | 24% | 17% | 16% | 30% | 31% |
| **N of lesions** | | | | | |
| **3** | 18% | 11% | N.A. | N.A. | N.A. |
| **4** | 24% | 29% | 28% | 31% | 36% |
| **5** | 12% | 6% | 14% | 19% | 23% |
| **6** | 12% | 11% | 19% | 12% | 13% |
| **7** | 9% | 11% | 7% | 14% | 13% |
| **8** | 24% | 33% | 33% | 24% | 15% |
| **Severity of lesions** | | | | | |
| **mild** | 43% | 44% | 46% | 42% | 45% |
| **moderate** | 57% | 56% | 54% | 58% | 55% |

In the main studies most patients were males with a mean age around 70, which is acceptable as the prevalence of AK is higher in males than females and occurs often in older age.

Severity of the lesions was equally distributed across the treatment groups. In study AK04, there were fewer females in the placebo group as compared to the active arms. However this is not a concern as gender did not influence efficacy.

The application duration of four hours in the pivotal trials was based on supportive studies AK01 and AK02.

Table 6 presents the results of the main studies AK03 and AK04. In terms of the most relevant endpoint, complete clearance of all lesions (*i.e.* responders), both studies reach statistically significant difference in efficacy between placebo and 5-ALA Regiomedica, showing superiority of the patch against placebo. Responder rate with 5-ALA Regiomedica is numerically larger than with cryosurgery and the difference is of borderline significance (p=0.0689), in favour of the patch.

**Table 6.** Results of the main studies AK03 and AK04

| | AK03 | | AK04 | | |
|---|---|---|---|---|---|
| | **Placebo** | **5-ALA** | **Placebo** | **5-ALA** | **cryosurgery** |
| **N** | 33 | 66 | 48 | 144 | 139 |
| **Lesion based clearance rate** | 19% | 82% | 32% | 87% | 77% |
| **Analysis*** | | | Placebo vs. 5-ALA | cryosurgery vs. 5-ALA | |
| **Difference** | 63.3% | | 55% | 10% | |
| **$CI_{95\%}$** | 55.7 – 69.5% | | 49.2% - 60.9% | 6.4% - 13.9% | |
| **p-value** | <0.0001 | | 0.0002 | 0.069 | |
| **Responder at 12 weeks*** | 6% | 62% | 12% | 64% | 53% |
| **Analysis** | | | Placebo vs. 5-ALA | cryosurgery vs. 5-ALA | |
| **Difference** | 56% | | 49% | 11% | |
| **$CI_{95\%}$** | 38% - 68% | | 34% - 60% | 1% - 22% | |
| **p-value** | <0.001 | | <0.0001 | 0.0689 | |
| **Recurrence-free, lesion basis** | | | | | |
| **12w - 6 mo** | 68% | 89% | 93% | 93% | 89% |
| **6 mo – 9 mo** | 56% | 81% | 92% | 89% | 85% |
| **9 mo – 12 mo** | 47% | 76% | 88% | 88% | 82% |
| **Recurrence-free, patient basis** | | | | | |
| **12w - 6 mo** | 0% | 75% | 86% | 87% | 84% |
| **6 mo – 9 mo** | | 60% | 86% | 78% | 75% |
| **9 mo – 12 mo** | | 52% | 86% | 73% | 71% |
| **Cosmetic outcome at week 12**, investigator** | | | | | |
| **Excellent** | 50% | 81% | 59% | 69% | 42% |
| **Good** | 50% | 15% | 34% | 30% | 49% |
| **Fair** | - | 1% | - | 1% | 8% |
| **Poor** | - | - | - | - | 1% |
| **Cosmetic outcome at week 12**, patient** | | | | | |
| **Excellent** | 50% | 76% | 66% | 67% | 43% |
| **Good** | 39% | 20% | 34% | 32% | 49% |
| **Fair** | 11% | - | - | 2% | 7% |
| **Poor** | - | - | - | - | 1% |

* Defined as complete clearance of all lesions

** Based on AK lesions which showed complete clinical clearance

In study AK03, gender, lesion size, lesion grade, lesion localization or skin type did not influence efficacy. In study AK04, gender, lesion size or skin type did not influence efficacy. Lesions graded moderate were more likely not to be cleared as compared to mild lesions. However this finding was driven by difference in clearance rates in the placebo group. Localization of the lesion on the ear influenced efficacy in a negative way. However, number of lesions on the ear was low.

In all the clinical trials with the 5-ALA patch, diagnosis of AK was not based on biopsy, but made visually. Misdiagnosis could have affected the rather high placebo response observed in study AK04 (responder rate 12%). The consistency of clinical diagnosis and biopsy appears to be high (~91%) (Ehrig et al, 2006[1]), therefore the lack of biopsy in the studies is agreed. The placebo response in the 5-ALA Regiomedica studies is within the known placebo response rate from other 5-ALA studies and clinical studies performed with other treatments. Also the response to cryosurgery in study AK04 is within the response reported in the literature.

In the studies, 5-ALA Regiomedica was superior to placebo in terms of complete clinical clearance on both lesion and patient basis. Complete clearance of lesions on patient basis is considered the most relevant endpoint. Complete clearance of all lesions is the desired treatment result for AK, since more

[1] Ehrig T, Cockerell C, Piacquadio D, Dromgoole S: Actinic keratoses and the incidence of occult squamous cell carcinoma: a clinical-histopathologic correlation. Dermatol Surg. 2006 Oct; 32(10): 1261-5

treatment sessions are required if a patient has numerous lesions from which only some are completely cleared.

Despite the differing inclusion criteria with respect to minimum number of lesions between studies AK03 and AK04, responder rates are comparable.

The recurrence rates are between 20% and 50%, and in particular in study AK04 are comparable between treatment groups. Recurrence rates in 5-ALA group were between 11% (lesion based) and 26% (patient based), which is comparable to what is reported from other topical 5-ALA containing products. No repeated dose studies were performed. Evidence from the literature shows that re-treatment of non-cleared lesion is efficacious, with approximately 20-66% clearance of lesions after second treatment. This will be addressed in the Risk Management Plan. Furthermore there are no safety concerns over re-treatment 3 months after the first treatment session with respect to local or systemic tolerability.

## IV.5 Clinical safety

With a topical product containing 5-ALA and subsequent photodynamic therapy, it is difficult to disentangle whether a local reaction is due to the treatment or a part of the wanted effect (tissue destruction). Local adverse reactions at the application site were common, which is expected with a topical 5-ALA product. Before illumination, about 30% of patients treated with 5-ALA Regiomedica suffered a local AE. During illumination, majority of patients, about 90%, had a local adverse reaction. Incidence of local adverse reactions is comparable to other products containing 5-ALA. 21% of patients in the 5-ALA patch group in studies AK03 and AK04 experienced a severe local adverse reaction as compared to 8% in the cryosurgery group.
In studies AK03 and AK04, very few local adverse reactions persisted beyond day 29 after treatment, based on patient diaries. During the follow-up period of 12 months in these studies, no adverse events were reported. The incidence of severe local reactions is comparable to other topical 5-ALA products.

In the SmPC and package leaflet, the patient is advised to avoid sun light for the treated skin and the surrounding skin area for a period of 48 hours after exposure to 5-ALA. Majority of the phototoxic PPIX will be destroyed at illumination. 5-ALA levels return to baseline within 24 hours after application of the patch, thus the amount of PPIX that will be formed within the 48 hour safety limit will be very little. Therefore extending the sunlight protection period beyond 48 hours, which is also a standard recommendation after photodynamic therapy, is not considered necessary.

## IV.6 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to 5-Aminolevulinezuur Regiomedica 8 mg, medicated plaster.

**Summary table of safety concerns as approved in RMP**

| Summary of safety concerns | |
|---|---|
| **Important identified risks** | Application site reactions |
| | Hypo-/hyperpigmentation at the treatment site |
| **Important potential risks** | Intensified local reactions after 5-ALA patch application for more than 4 h or after illumination with a light dose of more than 37 J/cm² |
| | Concomitant use of hypericin or other drugs with photosensitising properties |
| | Photogenotoxicity |
| | Reproductive and developmental toxicity |
| | Recurring lesions |
| **Missing information** | Off label use in conditions other than AK (e.g. basal cell carcinoma, acne, warts) and off label use as repeated treatment for not completely cleared lesions |
| | Patients with immunosuppression |

The member states consider that routine pharmacovigilance practice and appropriate product labelling are sufficient. The active substance is well known. Identified safety concerns for 5-ALA patch are consistent with the safety profile of other 5-ALA-containing medicinal products for PDT-treatment of AK. Routine pharmacovigilance is considered an adequate methodology for monitoring the safety profile and for providing a warning system should any new, to date unknown safety concerns arise.

### IV.7 Discussion on the clinical aspects

Efficacy of 5-ALA Regiomedica over placebo in the treatment of AK was established in studies AK03 and AK04, in relation to the most relevant efficacy endpoint, *e.g.* responder defined as patients whose lesions were completely cleared at week 12. Responder rate for 5-ALA Regiomedica in study AK03 was 62%, as compared to 6% for placebo (p=0.0001). In study AK04 the corresponding responder rates were 64% and 12% (p=0.0002). In study AK04, responder rate for cryosurgery was 53% (p vs. 5-ALA 0.069).
Although superiority to placebo has been shown in adequately blinded studies, non-inferiority or superiority to an existing treatment is difficult to assess. The choice of cryosurgery as a comparator in study AK04 is accepted as standard therapy but, by definition, cannot be blinded. The small numerical difference in responders between 5-ALA Regiomedica and cryosurgery could be due to observer's awareness of treatment. Magnitude of effect is comparable to other topical 5-ALA containing products, Ameluz and Metvix (60-80%). Superiority to cryosurgery is not claimed in the SmPC. The submitted clinical studies provide sufficient evidence of efficacy of 5-ALA Regiomedica. Superiority over placebo is considered sufficient for granting a marketing authorization, with the comparison to cryosurgery as supportive data.
The safety profile of 5-ALA Regiomedica is comparable to other topical 5-ALA products with respect to local adverse reactions, which were common as expected taking into account the mechanism of action of 5-ALA. Duration of adverse events was comparable to what is observed with other topical 5-ALA treatments, *i.e.* a few weeks at maximum. Risk management is adequately addressed. In conclusion, the benefit-risk balance is considered positive.

## V. USER CONSULTATION

The package leaflet (PL) has not been evaluated via a user consultation study. A bridging report has been submitted, making reference to the full user test on the English version of the PL for AlaCare 2 mg/cm$^2$ patch, also containing 5-ALA as active substance.
The differences in the English language version of the PLs for AlaCare and 5-Ala Regiomedica 8 mg are minor and have been explained.

The presentation of the information, style and layout follows the "house style" of Regiomedica, which has been successfully tested in procedures, *e.g.* for the parent PL of Irinotecan Regiomedica.

The requirements of Article 59(3)/Directive 2001/83/EC as amended by Directive 2004/27/EC are met and user readability has been demonstrated. The bridging is considered acceptable.

# VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

5-Aminolevulinezuur Regiomedica 8 mg, medicated plaster has a proven chemical-pharmaceutical quality. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

There were no issues concerning the non-clinical pharmacology or toxicology of 5-ALA HCl that negatively affected the overall benefit-risk assessment.

The approved indication is 'treatment of mild to moderate actinic keratoses (AK) lesions on the face and scalp (hairless areas)'. Clinical efficacy and safety have been demonstrated in a number of trials. The results demonstrate that the 5-ALA plasters are efficacious and can be used safely. Superiority over placebo was shown and no unexpected side effects were observed for this well-known active substance.

In the Board meeting of 1 August 2013, the submitted dossier was discussed. The Board expressed its positive opinion on the application for 5-AminolevulinezuurRegiomedica.

As the benefit-risk balance is considered positive, the member states have granted a marketing authorisation. There was no discussion in the CMD(h); agreement was reached through a written procedure. The decentralised procedure was finalised on 6 March 2014.

There were no post-approval commitments made during the procedure.

## STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

| Scope | Procedure number | Type of modification | Date of start of the procedure | Date of end of the procedure | Approval/ non approval | Assessment report attached |
|---|---|---|---|---|---|---|
| | | | | | | |