Public Assessment Report

Decentralised Procedure

Alacare 8mg Medicated Plaster

UK/H/1533/001/DC

UK licence no: PL 11587/0049

medac Gesellschaft für klinische Spezialpräparate mbH
LAY SUMMARY

On 23rd July 2009, the MHRA granted medac Gesellschaft für klinische Spezialpräparate mbH a Marketing Authorisation (licence) for the medicinal product Alacare 8mg Medicated Plaster (PL 11587/0049). This is a prescription only medicine (POM) for the treatment of mild skin abnormalities on the head or face called solar keratosis. These are small, rough, spots which develop on the skin. They are caused by a lot of exposure to the sun over many years. They are also called actinic keratosis.

Treatment with Alacare is a two-step procedure and is called ‘photodynamic therapy’. It consists of Alacare plaster application to the spots for 4 hours. This is followed by illumination with red light for a couple of minutes. Illumination with red light induces a chemical reaction in the cells of the changed skin, which leads to their destruction. The reaction is called ‘phototoxic reaction’.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Alacare 8mg Medicated Plaster (PL 11587/0049) outweigh the risks; hence a Marketing Authorisation has been granted.
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<td>Page 28</td>
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</table>
### Module 1 – Information about the initial procedure

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Alacare 8mg Medicated Plaster</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Article 8.3, Known Active Substance</td>
</tr>
<tr>
<td><strong>Active Substance</strong></td>
<td>5-aminolevulinic acid hydrochloride</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Medicated plaster</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>2mg per cm²; Total 8mg</td>
</tr>
<tr>
<td><strong>MA Holder in the UK</strong></td>
<td>Medac Gesellschaft Für Klinische Spezialpräparate MBH, Fehlandtstrasse 3, D-20354 Hamburg, Germany</td>
</tr>
<tr>
<td><strong>Reference Member State</strong></td>
<td>United Kingdom</td>
</tr>
<tr>
<td><strong>Concerned Member States</strong></td>
<td>Austria, Germany, Denmark, Spain, Finland, France, Ireland, Italy, Norway, Poland, Portugal, Sweden</td>
</tr>
<tr>
<td><strong>Procedure Number</strong></td>
<td>UK/H/1533/001/DC</td>
</tr>
<tr>
<td><strong>Timetable</strong></td>
<td>Day 210 – 8th June 2009</td>
</tr>
</tbody>
</table>
Module 2 - Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Alacare 8 mg medicated plaster

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each medicated plaster of 4 cm² contains 8 mg 5-aminolevulinic acid, 2 mg per cm².
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Medicated plaster.
Each plaster has a size of 4 cm², 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.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Single use treatment of mild actinic keratoses lesions with a maximum diameter of 1.8 cm on the face and scalp (hairless areas).

4.2 Posology and method of administration
Adults (including the elderly):
For the treatment of AK with one session photodynamic therapy (PDT), apply up to a maximum of six Alacare patches used on six different lesions to the patient on a single treatment session. If the Alacare plaster does not stick to the lesions properly, it can be fixed with an adhesive strip.

After four hours, remove the Alacare plaster(s) and expose the lesion(s) to red light with a narrow band red light source with a spectrum of 630 ± 3 nm and a total light dose of 37 J/cm² at the lesion surface. Only CE marked lamps should be used, equipped with necessary filters and/or reflecting mirrors to minimize exposure to heat, blue light and UV radiation. It is important to ensure that the correct light dose is administered. The light dose is determined by factors such as the size of the light field, the distance between lamp and skin surface and illumination time. These factors vary with lamp type, and the lamp should be used according to the user manual. Patient and operator should adhere to safety instructions provided with the light source. During illumination patient and operator should wear protective goggles which correspond to the lamp light spectrum.

Untreated skin surrounding the lesion does not need to be protected during illumination.

Lesion responses should be assessed after three months. If the area treated with Alacare is not lesion free at 3 months following single use please use alternative therapies for removal of actinic keratosis lesions.

Children and adolescents:
There is no experience of treating patients below the age of 18 years.

4.3 Contraindications
Hypersensitivity to the active substance or to the plaster material.
No response to previous PDT with 5 aminolevulinic acid-containing preparations.
Porphyria.

4.4 Special warnings and precautions for use
Alacare is not recommended for the treatment of pregnant women unless clearly necessary (see 4.6).

Very thick, red, scaly indurated AK lesions should not be treated with Alacare.

There is no experience of treating AK lesions in patients with dark brown or black skin (skin sun sensitivity type V or VI according to Fitzpatrick).

No data regarding efficacy and safety are available for repeated treatment of AK lesions with Alacare.
Any UV-therapy should be discontinued before treatment. As a general precaution, sun exposure of the treated lesion sites and surrounding skin should be avoided for approximately 48 hours following treatment.
Direct eye contact with Alacare should be avoided.

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.

4.5 Interaction with other medicinal products and other forms of interaction
As hypericin can increase phototoxic reactions induced by PDT, treatment with hypericin-containing products (St John's Wort, Hypericum perforatum) should be discontinued two weeks before PDT with Alacare.

4.6 Pregnancy and lactation
There are no adequate data from the use of 5-aminolevulinic acid in pregnant women. Animal studies are insufficient with respect to effects on pregnancy, embryonal and fetal development, parturition and postnatal development (see section 5.3). The potential risk for humans is unknown. Alacare should not be used during pregnancy unless clearly necessary.

It is unknown whether 5-aminolevulinic acid is excreted in human breast milk. The excretion of 5-aminolevulinic acid has not been studied in animals. Breast-feeding should be discontinued for 48h after application of Alacare.

4.7 Effects on ability to drive and use machines
None.

4.8 Undesirable effects

a) Almost all patients (99%) experience adverse reactions localised at the treatment site (local reactions) that are attributable to toxic effects of the photodynamic therapy (phototoxicity). During application of Alacare and prior to illumination of the treatment site, 33% of patients show local reactions, most frequently pruritus, burning and erythema. During illumination, erythema, burning and pain are the local reactions reported most often. The symptoms are usually of mild or moderate severity and require early termination of illumination in 1% of the patients. Cooling of the treated area may alleviate these symptoms. After therapy, pruritus, erythema, scabbing and exfoliation are the most frequent local reactions which are likewise mainly mild to moderate and persist for 1 to 2 weeks or occasionally longer.

A common (< 10%) adverse reaction not involving the treatment site is headache.

b) The incidence of adverse reactions in patients receiving Alacare plus illumination, is shown in the table below.

<table>
<thead>
<tr>
<th>Adverse reactions involving the treatment site (local reactions)</th>
<th>Very common</th>
<th>Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema, exfoliation, irritation, pain, pruritus, scab</td>
<td>≥ 1/10</td>
<td></td>
</tr>
<tr>
<td>Bleeding, desquamation, discharge, discomfort, erosion, hyper/hypopigmentation, oedema, reaction, swelling, vesicles</td>
<td>≥ 1/100, &lt; 1/10</td>
<td></td>
</tr>
<tr>
<td>Burn, discolouration, excoriation, inflammation, ulcer</td>
<td>≥ 1/1000, &lt; 1/100</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse reactions not involving the treatment site</th>
<th>Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>≥ 1/100, &lt; 1/10</td>
</tr>
<tr>
<td>Pyoderma</td>
<td></td>
</tr>
<tr>
<td>Emotional distress</td>
<td></td>
</tr>
<tr>
<td>Epistaxis</td>
<td></td>
</tr>
<tr>
<td>Skin discolouration</td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td></td>
</tr>
</tbody>
</table>
4.9 Overdose
No case of overdose has been reported. Nevertheless, reactions at the treatment site may be more pronounced if the Alacare plasters are applied for much more than 4 hours or if a much higher light dose than the recommended 37 J/cm² is chosen.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group:
Sensitisers used in Photodynamic/Radiation therapy, ATC Code: L01XD04

Mechanism of action:
After topical application of 5-aminolevulinic acid, protoporphyrin IX (PPIX) accumulates intracellularly in the treated AK lesions. 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.

Clinical efficacy and safety
With regard to clinical safety and efficacy, Alacare was compared with placebo treatment, in a randomised observer blinded clinical trial which enrolled 107 patients with a follow-up duration of 6, 9 and 12 months. All patients had a minimum of 3 mild to moderate AK lesions on the head and/or face. Alacare was applied to AK lesions for 4 hours without preparation of the lesion, after which they were illuminated with red light at $\lambda$ 630 ± 3 nm (37 J/cm²).

12 weeks after treatment, complete clinical clearance on lesion and on patient basis of a once-only photodynamic therapy with Alacare was statistically significantly more effective than photodynamic therapy with placebo. This was sustained during follow-up, in which patients were seen every 3 months (after 6, 9 and 12 months).

In an open randomised trial, which enrolled 349 patients, Alacare PDT in the same regime as described above, was compared with cryosurgery and placebo-PDT. In this trial, Alacare-PDT proved non-inferior to cryosurgery. After 12 weeks in the Full Analysis Set 87% of lesions treated with Alacare-PDT were cleared, compared to 77% after cryosurgery (Odds Ratio 1.86; 95% CI [1.18, 2.93]) and 32% after placebo-PDT. Differences were sustained during the complete follow-up period (after 6, 9 and 12 months). Recurrence rates of cleared lesions 12 months after therapy were 12% for Alacare-PDT and 18% for cryosurgery (Odds Ratio 0.627; 95% CI [0.461, 0.854]).

5.2 Pharmacokinetic properties
Pharmacokinetic data from a clinical trial in patients with mild to moderate actinic keratoses on the head and/or face, who had 8 Alacare plasters applied for 4h, showed a baseline corrected Cmax of 16.4 µg/L and an AUC0-24 of 101.4 µg*h/L of systemic exogenous 5-aminolevulinic acid. Tmax was at 4 hours. The excretion of 5-ALA in urine during the first 12 hours after application was low. The maximum excretion was 2.06 % of the total dose, the median was 1.39 %

PPIX was not detected in any of the plasma samples.

In another clinical trial in 12 AK patients with mild to moderate AK lesions on the head and/or face, it could be shown that Alacare-induced PPIX specific fluorescence is higher in AK lesions than in normal skin and increases with duration of the Alacare exposure. However, extending application interval beyond 4h did not result in higher PPIX fluorescence.

5.3 Preclinical safety data
Preclinical studies on general toxicity and genotoxicity studies in the presence or absence of photoactivation, do not indicate potential risks for man. Conventional carcinogenicity studies have not been performed with 5-aminolevulinic acid. Studies reported in the literature do not indicate a carcinogenic potential. Studies on the reproductive function have not been performed.
6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Plasters: Acrylic pressure sensitive adhesive
(Poly[(2-ethylhexyl)acrylate-co-methylacrylate-co-acrylic acid-co-glycidylmethacrylate])

Backing film: Pigmented polyethylene Aluminium vapor coated polyester

Release liner (polyethylene terephthalate film) which is removed prior to application.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years
Use within 3 months after first opening.

6.4 Special precautions for storage
After opening store plaster in the sachet in order to protect from light.

6.5 Nature and contents of container
4 medicated plasters sealed in protective sachets consisting of 4 layers: paper (outer layer), polyethylene LDPE, aluminium, ethylene copolymer (inner layer).

Pack sizes of 4 or 8 medicated plasters (1 or 2 protective sachet(s)).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
After removal, the used patch should be folded in half, adhesive side inwards so that the adhesive is not exposed, and then discarded safely.

7 MARKETING AUTHORISATION HOLDER
medac Gesellschaft für klinische Spezialpräparate mbH
Fehlandstraße 3,
20354 Hamburg
Germany

8 MARKETING AUTHORISATION NUMBER(S)
PL 11587/0049

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
23/07/2009

10 DATE OF REVISION OF THE TEXT
23/07/2009
Module 3 – Product Information Leaflets

PACKAGE LEAFLET: INFORMATION FOR THE USER

Alacare 8 mg medicated plaster
5-aminolevulinic acid

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

In this leaflet:
1. What Alacare is and what it is used for
2. Before you use Alacare
3. How to use Alacare
4. Possible side effects
5. How to store Alacare
6. Further information

1. WHAT ALACARE IS AND WHAT IT IS USED FOR

Alacare is used for the treatment of mild skin abnormalities on the head or face called solar keratosis. These are small, rough, spots which develop on the skin. They are caused by a lot of exposure to the sun over many years. They are also called actinic keratosis.

Treatment with Alacare is a two-step procedure and is called 'photodynamic therapy'. It consists of Alacare plaster application to the spots for 4 hours. This is followed by illumination with red light for a couple of minutes. Illumination with red light induces a chemical reaction in the cells of the changed skin, which leads to their destruction. The reaction is called 'phototoxic reaction'.

2. BEFORE YOU USE ALACARE

Alacare should be applied by a physician, a nurse or other health care professionals in one single session.

Do not use Alacare if you

- are allergic (hypersensitive) to 5-aminolevulinic acid, acrylic pressure sensitive adhesive or any of the other ingredients of Alacare.
- suffer from a certain disease of blood metabolism known as porphyria.
- were undergoing similar therapy with 5-aminolevulinic acid-containing preparations and it was unsuccessful.

Please ask your doctor if you are not sure.

Take special care with Alacare if you

- have dark brown or black skin or if you have very thick lesions since there is no experience with Alacare treatments in those cases.
- might be pregnant since treatment with Alacare is not recommended then.
- If you are receiving UV-therapy, it should be stopped before treatment with Alacare.

Please ask your doctor if you are not sure.

Your doctor or nurse will make sure that the Alacare plaster does not get into contact with your eyes. As a general precaution, treated and surrounding skin should not be exposed to sunlight for about 48 hours following treatment.

Taking other medicines

Please tell your doctor if you are taking or have recently taken any medicines, even those which were obtained without prescription.

It is important to inform your doctor if you are taking or have taken products containing St John’s Wort (Hypericum perforatum) or used products containing Hypericum on your skin in the last two weeks. This could increase the phototoxic reaction when it is given together with Alacare.

Pregnancy and breast-feeding

Possible harmful effects and risks for a pregnancy and for the unborn child cannot be completely excluded at this time. Alacare should not be used during pregnancy unless clearly necessary. Breast-feeding should be stopped for 48 hours after application of Alacare. Always ask your doctor for advice before taking any medicines.

Driving and using machines

Alacare has no known effect on the ability to drive and use machines.

3. HOW TO USE ALACARE

It is important that you do not apply any cream to your scalp or face on the day of treatment before arriving for therapy at your doctor.

Adults (including the elderly)
Alacare plasters will be applied to your actinic keratoses (changed skin) for 4 hours in one single session. Afterwards these areas will be exposed to red light for a few minutes (photodynamic therapy). To protect your eyes from the intense light, you will be given goggles to wear during light exposure.

After treatment with plaster and illumination you should protect the skin from sunlight for 48 hours. Lesions should be checked by your doctor after three months.

Children and adolescents
Use of Alacare is not recommended, as there is no experience in treatment of children and adolescents below 18 years of age.

If you want to stop using Alacare
The effectiveness of the treatment might be reduced, if
- plaster application is stopped prematurely or
- light therapy is stopped too early.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Alacare can cause side effects, although not everybody gets them.
Side effects involving the treatment site (local side effects)

Almost all patients (99%) experience side effects localised to the treatment site (local side effects). These can occur during application of the Alacare plaster, during illumination of the treatment site and/or thereafter. Symptoms are usually of mild or moderate intensity. They rarely require early termination of illumination. For relief, the treated area can be cooled by a fan or similar during illumination. After therapy, local side effects persist for 1 to 2 weeks or occasionally longer.

Very common (more than 1 out of 10 patients):
- flaking
- irritation
- itching
- pain
- redness
- scab

Common (more than 1 out of 100 patients, but less than 1 out of 10 patients):
- areas of paleness or darkening of the skin
- bleeding
- blister
- discomfort
- erosion
- oedema (fluid accumulated in the tissue)
- peeling
- pustules (pimples)
- skin reaction
- secretion
- swelling

Uncommon (more than 1 out of 1000 patients, but less than 1 out of 100 patients):
- burn
- staining
- infection
- inflammation
- ulcer
- superficial skin defects

Side effects not involving the treatment site:

Common
- headache

Uncommon
- anxiety
- increased levels of the enzyme alanine aminotransferase
- nosebleed
- pustule (pimple like) rash
- staining of the skin
If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

5. **HOW TO STORE ALACARE**

Keep out of the reach and sight of children.
Do not use Alacare after the expiry date which is stated on the carton and sachet after 'EXP'. The expiry date refers to the last day of that month.
Use within 3 months after first opening.
After opening store plaster in the sachet in order to protect from light. After removal, the used plaster should be folded in half, adhesive side inwards so that the adhesive is not exposed, and then discarded safely. Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. **FURTHER INFORMATION**

**What Alacare contains**

- The active substance is 5-aminolevulinic acid hydrochloride. Each medicated plaster of 4 cm$^2$ contains 8 mg 5-aminolevulinic acid (as hydrochloride), 2 mg per cm$^2$.
- The other ingredients are acrylic pressure sensitive adhesive, backing film, consisting of pigmented polyethylene and aluminium vapour coated polyester, release liner consisting of polyethylene/polyester film (to be removed before application).

**What Alacare looks like and contents of the pack**

Each medicated 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. 4 plasters are sealed in a protective sachet.
Alacare is available in pack sizes of 4 or 8 plasters (1 or 2 protective sachet(s)) in a cardboard box.

**Marketing Authorisation Holder and Manufacturer**

Marketing Authorisation Holder: medac Gesellschaft für klinische Spezialpräparate mbH
Fehlautstr. 3
20354 Hamburg, Germany

Manufacturer: LTS Lohmann Therapie-Systeme AG
Lohmannstraße 2
D-56626 Andernach
Germany

Intendis Manufacturing S.p.A.
Via E. Schering 21
20090 Segrate (Milan)
Italy

This medicinal product is authorised in the Member States of the EEA under the following names:

Austria | Alacare
Denmark | Alacare
Finland Alacare
France Effala
Germany Alacare
Ireland Alacare
Italy Alacare
Norway Alacare
Poland Alacare
Portugal Alacare
Spain Effala
Sweden Alacare
UK Alacare

This leaflet was last approved in

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## Module 4 - Labelling

<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS</th>
</tr>
</thead>
</table>

1. **NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

   Alacare® 8 mg medicated plaster  
   5-aminolevulinic acid

2. **METHOD OF ADMINISTRATION**

   Cutaneous use

3. **EXPIRY DATE**

   EXP:  
   Use within 3 months after first opening

4. **BATCH NUMBER**

   Lot:

5. **CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

   4 medicated plasters, each of 4 cm² contains 8 mg 5-aminolevulinic acid, 2 mg per cm².

6. **OTHER**

   medac Gesellschaft für klinische Spezialpräparate mbH
### PARTICULARS TO APPEAR ON THE OUTER PACKAGING

1. **NAME OF THE MEDICINAL PRODUCT**

   Alacare® 8 mg medicated plaster
   5-aminolevulinic acid

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

   4 [8] medicated plasters of 4 cm² contain 8 mg 5-aminolevulinic acid, 2 mg per cm².
   Acrylic pressure sensitive adhesive, backing film consisting of pigmented polyethylene and aluminium vapor coated polyester, release liner consisting of polyethyleneesterphthalate film (to be removed before application)

3. **LIST OF EXCIPIENTS**

4. **PHARMACEUTICAL FORM AND CONTENTS**

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

   Cutaneous use
   Read the package leaflet before use

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

   Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

   EXP.
   Use within 3 months after first opening.

9. **SPECIAL STORAGE CONDITIONS**

   After opening store plaster in the sachet in order to protect from light.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**
11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

medac Gesellschaft für klinische Spezialpräparate mbH  
Fehlaustr. 3  
20354 Hamburg, Germany

12. **MARKETING AUTHORISATION NUMBER(S)**

MA no.: PL 11587/0049

13. **BATCH NUMBER**

Lot:

14. **GENERAL CLASSIFICATION FOR SUPPLY**

POM

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

Alacare 8 mg medicated plaster
Module 5 - Scientific discussion during initial procedure

I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted a marketing authorisation for the medicinal product Alacare 8mg Medicated Plaster (PL 11587/0049) on 23rd July 2009. The product is a prescription-only medicine as a single-use treatment of mild actinic keratoses lesions with a maximum diameter of 1.8 cm on the face and scalp (hairless areas).

This application was made via the decentralised procedure, under Article 8.3 of 2001/83 EC, as amended, with the UK as Reference Member State (RMS) and Austria, Denmark, Finland, France, Germany, Ireland, Italy, Norway, Poland, Portugal, Spain and Sweden as Concerned Member States (CMSs). The decentralised procedure was successfully completed, with the end of procedure (Day 210) on 8th June 2009.

Alacare 8mg Medicated Plaster contains 2mg 5-aminolevulinic acid (as hydrochloride) per cm² as active ingredient. The product to be marketed is 4cm², containing a total of 8mg of drug substance, is square with rounded corners and consists of a skin tone backing foil and a 5-aminolevulinic acid (5-ALA)-containing self-adhesive matrix, covered by a release liner that is removed prior to use.

5-ALA is an endogenous compound and plays a significant role as precursor in the biosynthesis of, for example, hemoglobin or cytochrome C1. Intracellularly, 5-ALA is metabolised to protoporphyrin IX (PPIX), which has fluorescent properties. The exogenous application of 5-ALA leads to a highly selective accumulation of PPIX in, for example, (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 are formed. These reactive oxygen species cause damage to cells and tissues, resulting in apoptosis and tumour necrosis. This mechanism is used in PDT for the destruction of malignant and premalignant tissue. 5-ALA is indicated for single-use treatment of mild actinic keratoses lesions with a maximum diameter of 1.8 cm on the face and scalp (hairless areas).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of this product.

The manufacturing sites are only within the Community and the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The application was discussed by the MHRA Commission on Human Medicines on 22nd and 23rd May 2008, from which advice was issued. This advice was included in the points raised by the UK at Day 70 of the procedure. The marketing authorisation holder’s response to this advice and assessment of the response is incorporated into the preclinical and clinical section of this report, Sections III.2 and III.3, respectively. All points raised were resolved, leading to the grant of a licence for the indications stated in the current SPC (see Module 2).
II. ABOUT THE PRODUCT

Name of the product in the Reference Member State: Alacare 8mg Medicated Plaster

Name(s) of the active substance(s) (INN): 5-aminolevulinic acid hydrochloride

Pharmacotherapeutic classification (ATC code): Sensitisers used in photodynamic/radiation therapy (L01 XD04)

Pharmaceutical form and strength(s): Medicated Plaster, 2mg per cm²; Total 8mg

Reference numbers for the Decentralised Procedure: UK/H/1533/001/DC

Reference Member State: United Kingdom

Member States concerned: Austria, Germany, Denmark, Spain, Finland, France, Ireland, Italy, Norway, Poland, Portugal, Sweden

Marketing Authorisation Number(s): PL 11587/0049

Name and address of the authorisation holder in UK: medac Gesellschaft für klinische Spezialpräparate mbH, Fehlandstraße 3, 20354 Hamburg, Germany
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN: 5-aminolevulinic acid hydrochloride
Chemical Name: 5-Amino-4-oxo-pentaneacid hydrochloride
δ-Aminolevulinic acid hydrochloride
5-ALA*HCl; 5-ALA; 5-Aminolevulinic acid
CAS-Number: 5451-09-2
Molecular Formula: C₅H₉NO₃.HCl

Molecular Weight: 167.61
Appearance: White to off-white crystalline powder is freely soluble in water and slightly soluble in ethanol and methanol.

Synthesis of the drug substance from the designated starting materials has been adequately described, and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

All potential known impurities have been identified and characterised. Appropriate proof-of-structure data has been supplied for the active pharmaceutical ingredient.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Specifications for all packaging used have been provided and are satisfactory. A declaration has been provided that the primary packaging complies with current European regulations concerning contact with foodstuff.

A suitable retest period has been determined, based on the stability data submitted. All stability data was generated from studies conducted in accordance with ICH guidelines.

P Medicinal Product

Other Ingredients

In addition to the active substance, 5-aminolevulinic acid hydrochloride, the following “excipients” are also used in the product:

Plasters: Acrylic pressure sensitive adhesive
(Poly[(2-ethylhexyl)acrylate-co-methylacrylate-co-acrylic acid-co-glycidylmethacrylate])

Backing film: Pigmented polyethylene Aluminium vapor coated polyester

Release liner (polyethylene terephthalate film) which is removed prior to application.

All “excipients” used comply with suitable in-house specifications. Satisfactory certificates of analysis have been provided for all “excipients”. Confirmation has been provided that the backing film and release liner comply with the EU Plastics Directive 2002/72/EC and amendments. In addition, confirmation has been provided that the release liner complies with current European Pharmacopoeia requirements for medicated plasters.
None of the excipients used contain materials of animal or human origin.

**Pharmaceutical Development**
The applicant has provided a suitable product development rationale.

**Manufacture**
Satisfactory batch formulae have been provided for the manufacture of the product along with an appropriate account of the manufacturing process. Suitable in-process controls are applied during the manufacturing process to ensure the quality of the product.

The manufacturing process has been validated and has shown satisfactory results.

**Control of Drug Product**
The finished product specification proposed is acceptable and provides an assurance of the quality of the finished product. It complies with ICH Q6A “Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances” and the current European Pharmacopoeia regulations concerning medicated plasters.

The analytical methods used have been suitably validated. Batch analysis data have demonstrated compliance with the proposed specification.

Satisfactory data on the characterisation of impurities have been provided.

**Reference Standards or Materials**
Certificates of analysis for all reference standards used have been provided and are satisfactory.

**Container Closure System**
Four medicated plasters sealed in protective sachets consisting of four layers: paper (outer layer), polyethylene LDPE, aluminium, ethylene copolymer (inner layer). Pack sizes are 4 or 8 medicated plasters (1 or 2 protective sachet(s)).

The marketing authorisation holder has stated that they might not market all pack sizes. However, they have committed to submitting any mock-ups to the regulatory authorities before marketing a pack size.

Specifications and Certificates of Analysis for the primary packaging material have been provided. These are satisfactory. All primary packaging is controlled to European Pharmacopoeia standards and comply with guidelines concerning materials in contact with food.

**Stability of the Drug Product**
Stability data provided support a shelf-life of 3 years for the unopened product and 3 months once opened, with the storage instructions “After opening, store plaster in sachet to protect from light”.


SPC, PIL, Labels
The SPC, PIL and labels are pharmaceutically acceptable.

The PIL is in compliance with current guidelines and user testing results have been submitted. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

CONCLUSION
It is recommended that a marketing authorisation is granted for this application.

III.2 PRE-CLINICAL ASPECTS
Pharmacology
The pre-clinical pharmacology dossier, which comprises data generated by the applicant and supportive literature references, presents the scientific rationale and justifies the proposed use of 5-ALA in treatment of actinic keratosis. The applicant 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 dossier is based on literature references. The five published studies cited provide a satisfactory illustration of the secondary pharmacodynamic profile of 5-ALA. As there is adequate clinical experience 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 dog were considered to be linked to intravenous dosing and were reversible. On consideration of the proposed route of administration (dermal), it is unlikely that these findings are of significance.

No drug-interaction studies have been performed by the applicant. The results of pharmacodynamic drug interactions studies described in the literature do not indicate interactions that would have a significant negative influence on the clinical use of 5-ALA.

Pharmacokinetics
The pharmacokinetic profile of 5-ALA was described using studies conducted by the applicant and literature publications. 5-ALA is well-absorbed after oral and intravenous administration. Its absolute bioavailability in dogs is about 86% after administration of a 20mg/kg dose. The pharmacokinetic profile of 5-ALA orally administered to dogs and humans is similar after equivalent doses (20mg/kg), however, differences are seen in PPIX concentrations where PPIX levels were higher in humans in dogs. No pre-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 eight patches in patients with actinic keratosis lesions and after oral administration of 20mg 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 hours 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.

**Toxicology**

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 NOEL of 5-ALA in acute toxicity studies is several hundred fold above the intended topical administration dose in patients.

The most notable treatment-related changes in rats and dogs following repeat-dose oral and intravenous administration of 5-ALA for 14 days included increased liver weight, discoloration, bile duct changes and changes in clinical biochemistry. The liver was identified as the target organ. The bile duct changes were not reversible within a 14-day recovery period. No NOAEL was established as adverse effects were observed at the lowest doses tested, therefore, NOAEL values are below 30mg/kg (rat, oral), 125mg/kg (rat, intravenous), 3mg/kg (dog, intravenous).

The repeat-dose toxicity studies are of short duration (up to 14 days), which could be acceptable when considering the proposed treatment as a single-use topical product. Human systemic exposure to 5-ALA after intended single, topical application of the product is low compared to systemic exposure in oral and intravenous repeat-dose toxicity studies in rats and dogs.

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. No clinical evidence of higher skin cancer rates in patients with photosensitivity diseases exists.

However, as this product is to be used repeatedly in patients with recurrent actinic keratosis, more information was requested to determine the effect of long-term use on the mechanism of action with respect to selective toxicity. The applicant has conducted a 4-week local tolerance study of PD P 506 A in minipigs, following repeated epicutaneous application on intact and scarified skin (study no. 23397). Each animal was treated with the Alacare 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.

The *in vitro* and *in vivo* genotoxicity tests performed by the applicant 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.

In clinical use, a local phototoxic effect at the treatment site is desired for removal of the actinic keratosis lesion, however, a local photogenotoxic effect cannot be completely ruled out. Precautionary light protective measures of the treated area are recommended in the SPC, despite the likelihood that all PPIX will undergo photobleaching during PDT.

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. The lack of reproductive toxicity studies is considered to be acceptable bearing in mind the limited adsorption, the safety profile following intravenous dosing and the fact that 5-ALA is a naturally occurring cell constituent. Appropriate warnings have been included in the SPC sections 4.4 and 4.6.

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 pre-clinical 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 actinic keratosis 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 applicant has recommended in the SPC that the treated skin area be protected from light after PDT to avoid any additional local phototoxic reactions.

No pre-clinical concerns were raised in relation to skin sensitization. However, it was considered that local tolerance should be investigated in an appropriate species. In response to this, the applicant has conducted a local tolerance study of PD P 506 A in Minipigs following single epicutaneous application on intact and scarified skin (Report No. 23396), which demonstrated that no difference in local tolerance reactions, histopathology or macroscopic findings were observed when comparing the test and control patch.

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.

Studies have revealed 5-ALA to be phototoxic *in vivo*. Given the primary pharmacodynamic effect (induction of phototoxic damage in skin lesions), this is not surprising and pre-clinical findings are in accordance with clinical data.

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.
An acceptable justification 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), has been provided. Appropriate attention has been paid to the proposed disposal of the patch and associated wordings in the product particulars.

III.3 CLINICAL ASPECTS

Pharmacokinetics
The submitted study shows that some 5-ALA is absorbed and is available systemically. A peak plasma level, which corresponds to 1.5-times the pre-dose level, was recorded in 10 of the 12 patients. Unfortunately, the applicant did not compare to Metvix, so comparative evaluation to the first product of this class is not possible. No serious safety concerns were noted. Erythema and pruritus have been associated with this class of therapy.

Pharmacodynamics
The results show a time-dependent increase in fluorescence, which can be interpreted as accumulation of PPIX. Increasing the application duration from 4 to 5 hours does not further increase fluorescence. The fluorescence in actinic keratosis lesions is more intense than in normal skin, which further supports the specificity of 5-ALA for dysplastic cells. When observing the fluorescence over a period of 48 hours, the fluorescence level in healthy skin and primarily in actinic keratosis lesions 48 hours after removal of PD P 506 A still exceeds baseline. These findings represent a certain phototoxic potential, which in a clinical setting is of reduced importance as all PPIX molecules will be destroyed (i.e. bleached) by PDT illumination.

The incidence of erythema and pruritus at the application site were observed with three patients.

Clinical efficacy and Clinical safety
The applicant has submitted three studies to support the efficacy claim for PD P 506 A-PDT (Alacare). Of these three studies, only two (AK 02 and AK 03) appear to have been done in an observer-blinded fashion. AK 04 was done in an open manner and as such can only be considered observational. Study AK 02 was a time-ranging study designed to indicate the optimal time of exposure to PD P 506 A-PDT (Alacare). AK 03 is the only pivotal phase III study and, as such, provides an adequate (but minimal) amount of data needed to understand the effectiveness of this product versus placebo. This study shows that the Alacare patch effectively treats actinic keratosis after being placed for 4 hours on the lesion. The only source of concern as a confounder would be that half of the lesions were cleaned prior to application of the patch. The effect of this on efficacy has been explained by the applicant. All studies have submitted data on mild to moderate lesions, but no information on effectiveness on severe lesions. For this reason, this population has been excluded from the indication. The moderate population has been also excluded since no repeat-use data has been submitted in an effort to limit the perceived risk of conversion to squamous-cell carcinoma.

Based on this rationale, a single pivotal study has been considered (AK03) to support approval of Alacare. No data on the need for repeat dosing has been given.

The applicant has responded to the major concerns raised by the concerned member states by submitting recurrence rate data at 12 months compared to placebo and cryotherapy (AK03 and AK04, respectively). Both AK 03 and AK 04 were controlled studies, where the primary efficacy parameter was measured to 3 months, after which there was a 9-month, controlled follow-up period. AK 03 was double-blind for the first 3 months and then single-blind (observer-blind) thereafter. The data from both studies reproduce a similar recurrence rate seen with other similar therapies using 5-ALA, as presented by a literature review the
applicant has subsequently submitted. In addition, the 12-month data with Alacare is similar to those seen with cryotherapy (as seen in study AK04). The applicant has also submitted a literature review comparing the data generated in their studies with published data for Metvix cream, which has been available in Europe for almost 10 years. This supports efficacy and safety claims made in response to major concerns raised by the CMSs.

It should be noted that the average number of patches used in Study AK03 was 5.7 (or 6).

**Medical Assessor’s Conclusions:** Follow-up data submitted by the company at 12 months show that there was higher lesion-free percentage of patients with Alacare than with placebo and that this is similar to cryotherapy. The data are in-line with the literature review that the company has subsequently submitted. This is satisfactory providing the company accepts two points:

1. A limitation to the indication restricting use to only mild versions of actinic keratosis.
2. The company must accept a limitation to single use and a maximum number of six patches used on six different lesions in Section 4.2 of the SPC.

**Statistical Assessor’s Conclusions:** There is very strong evidence for the superiority of Alacare over placebo. Even though there are reservations regarding the method used for analysis, the magnitude of the difference is such that further re-analyses are considered unnecessary. The clinical trial data have established non-inferiority of Alacare in comparison to cryotherapy.

**Clinical safety**
The studies AK02, AK03 and AK04 have generated adverse events. These are very similar to those seen with Metvix, which belongs to the same class of compound. There is, however, a great variability in the reporting rates of local reactions during application of Alacare. Adverse reactions at the application site were observed in 11% (AK 02), 34% (AK 04) and 42% (AK 03) of the patients in the 4-hour Alacare treatment groups. The most common adverse events are local (erythema, pruritus and pain). There were cases of these events during illumination appearing as severe local adverse reactions (12 cases of severe local erythema, 38 cases of severe local irritation, 18 cases of severe local site pain and 4 cases of severe local pruritus). There were no deaths and there were no attributable cases of systemic adverse events. The product has a similar adverse event profile to Metvix. No long-term data, beyond 1 year of follow-up, has been submitted. No conversions to squamous cell carcinoma were observed after 1 year of follow-up, however, a reduction of malignancy has not been established.

**Pharmacovigilance system**
The pharmacovigilance system as described by the applicant fulfils the requirements, and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction suspected of occurring either in the European Community or in a third country.

**Risk Management Plan**
A suitable risk management plan has been submitted for this application.

**Periodic Safety Update Report (PSUR)**
The applicant has not requested a different PSUR cycle upon approval. The PSUR submission scheme will follow Volume 9A of The Rules Governing Medicinal Products in the European Union starting with 6-monthly PSUR.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Alacare 8mg Medicated Plaster are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
A literature review of published primary and secondary pharmacodynamic studies provide an adequate illustration of the pharmacodynamic profile of 5-ALA. The literature do not indicate any drug interactions that would have a significant negative influence on the clinical use of 5-ALA. Results of the toxicology studies did not identify any properties likely to cause toxicity in humans when the product is used as directed in the SPC.

EFFICACY
The indication is for the single-use treatment of mild actinic keratoses lesions with a maximum diameter of 1.8 cm on the face and scalp (hairless areas). The efficacy data submitted show that this product is suitable for the proposed indications.

SAFETY
No clinically significant safety concerns were identified. The product has been shown to have a similar adverse event profile to Metvix Cream.

BENEFIT-RISK ASSESSMENT
Alacare patches contain 5-ALA, which is used in photodynamic therapy for the treatment of actinic keratosis. Actinic keratosis lesions have a 0.1% per year probability of progressing to squamous cell carcinoma. Treatment of these lesions is, therefore, warranted in view of the difficulty of treating this form of cancer. The results from data submitted by the applicant satisfy the stipulations in CPMP/EWP/2330/99 and show the product is sufficiently more effective than placebo.

The product is only applied once in the treatment phase. The safety data generated in the file through studies AK 02, AK 03 and AK 04, as well as AK 05 (pharmacokinetics), have not generated any serious of life-threatening safety signals that would indicate that this product should not be approved. The safety profile is very similar to Metvix, which belongs to the same class of compound. No deaths were reported. Serum levels, although they reach 1.5-times the baseline value following application, are not associated with adverse events that can be considered serious or life-threatening. No PPIX appears in the serum. The data submitted support the licensing of this product as a single-use treatment only.

The current data set has limitations that must be taken into consideration when making the benefit-risk analysis. Although 5-ALA has been used in other formulations for a decade in Europe and the US, the data set submitted only establishes single-use efficacy and safety in mild to moderate patients. The applicant has submitted follow-up clearance rate data at 12 months, as well as bridging with data available in the literature, which helps clarify the place of Alacare patches in the treatment of lower-risk patients, such as those with mild actinic keratosis. Assessment of the benefit-risk in the moderate to severe actinic keratosis patients was performed on stratified data. Following assessment of this data, for a positive benefit-risk balance to be acceptable, the following conditions have been placed:
1. A limitation to the indication, restricting use to only mild versions of Actinic Keratosis.
2. A limitation to single-use and a maximum number of six patches used on six different lesions.
Module 6
STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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