A dermal application of 5-ALA for photodynamic therapy (PDT)
The indication: Actinic keratosis

Actinic keratosis in the EU

• Actinic keratosis (AK) = pre-cancerous lesion/SCC in situ
• More than 42 million people affected

Current treatment modalities

• Cryosurgery
• Topical creams (Effudix, Aldara, Solaraze)
• Photodynamic therapy
Photodynamic Therapy (PDT)

- Therapeutic use of a photochemical reaction
- First clinical application 1903 in Munich
- PDT mechanism:

\[ \text{Photosensitizer} \rightarrow \text{Ground state oxygen} \rightarrow \text{Singlet oxygen} \rightarrow \text{Absorption} \rightarrow \text{Energy transfer} \rightarrow \text{Cytotoxic reactions} \rightarrow \text{Necrosis or Apoptosis} \]
PDT with 5-ALA HCl

- 5-ALA HCL = 5-Aminolevulinic acid hydrochloride
  - produced naturally in the body
  - an early intermediate stage in the synthesis of haem
  - surplus of 5-ALA HCl lead to selective accumulation of protoporphyrin IX (PPIX) in diseased cells
  - PPIX: actual photosensitizer

[Chemical structure of 5-ALA HCl and PPIX]
Penetration of light into skin

PPIX absorption bands

λ [nm]
200 400 550 600 700

Epidermis
1 mm

Dermis
3 mm

Subcutaneous fat tissue

to see. to know. to heal.
Photodynamic Therapy

Current topical PDT procedures involve ...

- Preparation of the lesion(s) by curettage
- Application of the precursor in semiliquid formulation
- Occlusion with clingfilm
- Light protective measures
- Incubation
- After incubation: Cleaning of lesion(s)
- Illumination
Alacare® 8 mg medicated plaster

Product profile Alacare®

- Easy and convenient handling in a few steps
  - Apply, remove, illuminate!
  - No extra light protection necessary
  - Time saving for doctors and nurses as compared with standard PDT
- Defined dosage of the active ingredient
- Stable at room temperature (achieved: 3 years)
- Potential self application by patient
- Patent protected
**Alacare®: Pharmaceutical Development**

- Development of formulation
  - Manufacturing principle
  - Polymer
  - Particle size
  - Loading
- Development of analytical methods
- Development of manufacturing process
- Stability studies
Alacare® 8 mg medicated plaster

View on the release liner

Cross section through a single STS

- Skin coloured backing
- Polymer matrix with susp. of 5-ALA-HCl
- Release liner

5-ALA HCl crystals suspended in the polymer matrix

to see. to know. to heal.
Excipients

- Plaster:
  - Polyacrylic pressure sensitive adhesive

- Backing film:
  - Pigmented polyethylene Aluminium vapour coated polyester

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

- 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)).
Alacare® 8 mg medicated plaster
Alacare® 8 mg medicated plaster
Alacare®: Nonclinical development

Non-clinical experiments

Photonamic has performed
- safety pharmacology tests
- systemic general toxicity tests, including toxicokinetics and genotoxicology tests for 5-ALA and
- local tolerance tests for Alacare®

Preclinical pharmacodynamic tests
- have not been performed by photonamic as the principle of 5-ALA-PDT is well-known
- instead, literature data have been summarized in the CTD
Alacare®: Clinical development

**Indication under investigation in clinical trial program**

- Mild to moderate actinic keratosis of head and face*
- Maximum of 8 lesions per patient (package size)
- No pre-treatment of lesions (debulking) prior to patch application
- Single treatment (in conjunction with red light)
- Follow-up periods 8 weeks to 12 months
- Primary endpoint: lesion-based clearance rate
- Secondary endpoint: patient-based clearance rate

## Severity grade acc. to Cockerell

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition according to Cockerell</th>
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<tbody>
<tr>
<td>Mild (grade I)</td>
<td>Flat, pink maculae or patch on sun-damaged skin, background mottling, no roughness or hyperkeratosis</td>
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<tr>
<td>Moderate (grade II)</td>
<td>Pink to red papule or plaque with rough, hyperkeratotic surface, variable induration</td>
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<tr>
<td>Severe (grade III)</td>
<td>Red, scaly indurated plaques on sun-damaged skin; may be pigmented; very thick</td>
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Alacare® application interval: AK 01

- Fluorescence analysis study (no illumination)
- PPIX specific fluorescence in AK lesions steered by patch application duration
- No significant increase of fluorescence at time of patch removal between 4h and 5h application
- Application safe and well tolerable

Fauteck JD, Ackermann G, Birkel M et al., Arch Dermatol Res 300, 2008: 53-60
Alacare® application interval: AK 02

- Dose finding study (illumination with red light after patch removal)
- Lesion clearance rate after 8 weeks: 86% with 4h patch application
- 4h group statistically superior to the other arms

Alacare® pharmacokinetics: AK 05

- PK study (no illumination)
- 12 patients with 8 plasters (4h)
- 10/12 patients show maximum 5-ALA plasma levels greater than 1.5 x baseline
- Maximum plasma level: 3.7 x baseline values
- No detection of PPIX in plasma
- Application safe and well tolerable

Fauteck JD, Ackermann G, Birkel M et al., Arch Dermatol Res 300, 2008: 53-60
Confirmative phase III studies

AK 03:

• Alacare-PDT versus placebo-PDT (superiority design)
• Observer-blinded randomised parallel group comparison

AK 04:

• Alacare-PDT versus cryosurgery (non-inferiority design) and placebo-PDT
• Randomised parallel group comparison
Confirmative Phase III Studies

Number of patients
• 449 patients treated (2537 study lesions)
  – AK 03: 103 patients (587 lesions)
  – AK 04: 346 patients (1950 lesions)

Study treatments
• Comparison of treatment efficacy 12 weeks after therapy
• Follow-up until 12 months
• PDT: 4 h patch application plus standardized illumination protocol (37 J/cm² at λ 630 nm; red light)
• Cryosurgery: 5-10 sec after ice ball formation (mean: 7.3 sec)
Study populations AK 03 & AK 04

AK 03 (vs. Placebo)

- **Lesions**
  - 44% mild, 56% moderate
  - 52% forehead, 26% scalp, 12% cheek

- **Patients**
  - Mean age 70.7 years
  - 82% male
  - 92% skin type I or II*
  - Mean 5.7 AK study lesions

AK 04 (vs. Cryosurgery)

- **Lesions**
  - 44% mild, 56% moderate
  - 45% forehead, 29% scalp, 15% cheek

- **Patients**
  - Mean age 70.5 years
  - 72% male
  - 83% skin type I or II*
  - Mean 5.6 AK study lesions

*remaining: skin type III to see. to know. to heal.
AK 03: Clear superiority over placebo

Clearance rate 12 weeks after therapy [%]

Lesion based

Patient based

Alacare: 82% (star) vs. Placebo: 19%

Alacare: 62% vs. Placebo: 6%

Statistically significantly superior to placebo (p<0.0001)
AK 03: Clear superiority over placebo

Clearance rate 12 **months** after therapy [%]

*Lesion based*

- **Alacare**: 63%
- **Placebo**: 9%

*Statistically significantly superior to placebo (p<0.001)*

*Patient based*

- **Alacare**: 32%
- **Placebo**: 0%

*No statistical test possible*
AK 04: Clearance rates after PDT prove superior to cryosurgery

Clearance rate 12 weeks after therapy [%]

Lesion based

Patient based

Statistically significantly superior to cryosurgery (p=0.007) and placebo (p<0.001)

Statistically significantly superior to cryosurgery (p=0.02) and placebo (p<0.0001)

to see. to know. to heal.
AK 04: Clearance rates after PDT prove superior to cryosurgery

Clearance rate 12 months after therapy [%]

Lesion based

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<th>Treatment</th>
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Patient based

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Statistically significantly superior to cryosurgery and placebo (p<0.001)

Statistically significantly superior to cryosurgery (p=0.027) and placebo (p<0.001)
Alacare®-PDT: Summary of tolerability

Adverse reactions involving the treatment site:*

- *Very common*: Erythema, exfoliation, irritation, pain, pruritus, scab
- *Common*: Bleeding, desquamation, discharge, discomfort, erosion, hyper/hypopigmentation, oedema, reaction, swelling, vesicles, pustules

Adverse reactions not involving the treatment site:*

- *Common*: Headache

*Based on a safety meta analysis of all Alacare® efficacy studies (*unpublished data*)
Publications in peer reviewed journals

- **Fluorescence analysis study and PK study**

- **Dose finding study**

- **Phase III studies: 12 weeks data**

- **Phase III studies: 12 months data**
Alacare® 8 mg medicated plaster: Advantageous product profile

Summary

• Consistently high clearance rates after Alacare-PDT in 3 independent studies (82% to 89%) with a total of 1392 lesions treated with Alacare-PDT in 252 patients

• Clinical efficacy of Alacare superior to cryosurgery (and placebo) over a 12 months follow-up period

% Lesion clearance

Alacare AK 02 86
Alacare AK 03 82
Alacare AK 04 89
Cryosurgery 77
Placebo AK 03 19
Placebo AK 04 29

to see. to know. to heal.
Alacare® 8 mg medicated plaster: Advantageous product profile

- Excellent cosmetic results without scarring or altered pigmentation (superiority over cryosurgery)
- Simple, quick and convenient procedure
  - No debulking prior to Alacare application
  - No extra occlusion by clingfilm
  - No light protection
  - Cosmetically compatible plaster
  - No rinsing of the treated area after Alacare removal
  - “Simply apply it, remove it, illuminate it”
Alacare® 8 mg medicated plaster: Advantageous product profile

- Patient independent from doctor’s office during Alacare application interval
- Product potential: Self-administration by patient
- Defined 5-ALA dosage in each Alacare plaster
- Alacare suitable for difficult-to-treat areas (e.g. nose, ear)
- Larger areas (field cancerization; up to 32 cm²) can be treated by applying Alacare plasters adjacently
Alacare®: Status

- Registered in 2009 (European Decentralised Procedure) for PDT of up to 6 mild actinic keratoses lesions with a maximum diameter of 1.8 cm on the face and scalp (hairless areas)

- Marketed in Europe by Galderma
Alacare®-PDT has the potential to become first-line treatment in the therapy of Actinic Keratosis.
Thank you!

to see. to know. to heal.