ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
1. NAME OF THE MEDICINAL PRODUCT

Ameluz 78 mg/g gel

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One gram (g) gel contains 78 mg of 5-aminolaevulinic acid (as hydrochloride).

Excipients with known effect

One gram gel contains 2.4 mg sodium benzoate (E211), 3 mg soybean phosphatidylcholine, and 10 mg propylene glycol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gel.

White to yellowish gel.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of actinic keratosis of mild to moderate severity on the face and scalp (Olsen grade 1 to 2; see section 5.1) and of field cancerization in adults.

Treatment of superficial and/or nodular basal cell carcinoma unsuitable for surgical treatment due to possible treatment-related morbidity and/or poor cosmetic outcome in adults.

4.2 Posology and method of administration

Ameluz should only be administered under the supervision of a physician, a nurse or other healthcare professional experienced in the use of photodynamic therapy.

Posology in adults

For treatment of actinic keratoses (AK), one session of photodynamic therapy shall be administered for single or multiple lesions or entire fields with cancerization (areas of skin where multiple AK lesions are surrounded by an area of actinic and sun-induced damage within a limited field). Actinic keratosis lesions or fields shall be evaluated three months after treatment. Treated lesions or fields that have not completely resolved after 3 months shall be retreated.

For treatment of basal cell carcinoma (BCC), two sessions of photodynamic therapy shall be administered for one or multiple lesions with an interval of about one week between sessions. Basal cell carcinoma lesions shall be evaluated three months after last treatment. Treated lesions that have not completely resolved after 3 months shall be retreated.

Illumination dose: The entire treatment area, for both AK and BCC, shall be illuminated with a red light source, either with a narrow spectrum around 630 nm and a light dose of approximately 37 J/cm² or a broader and continuous spectrum in the range between 570 and 670 nm with a light dose between 75 and 200 J/cm². 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 the illumination time. These factors vary with lamp type. The light dose delivered should be monitored if a suitable detector is available.

Paediatric population

There is no relevant use of Ameluz in the paediatric population. No data are available.

Method of administration

Ameluz is for cutaneous use.

Preparation of the lesions: Before administration of Ameluz, all lesions should be carefully wiped with an ethanol or isopropanol-soaked cotton pad to ensure degreasing of the skin. Scales and crusts should be removed accurately and all lesion surfaces roughened gently. Care should be taken to avoid bleeding. Nodular BCC lesions are often covered by an intact epidermal keratin layer which should be removed. Exposed tumour material should be removed gently without any attempt to excise beyond the tumour margins.

Application of the gel: Ameluz should be applied to the lesion area or entire cancerized fields of about 20 cm², using glove protected fingertips or a spatula. The gel should cover the lesions or entire fields and approximately 5 mm of the surrounding area with a film of about 1 mm thickness. The gel should be allowed to dry for approximately 10 minutes, before an occlusive light-tight dressing is placed over the treatment site. Following 3 hours of incubation, the dressing should be removed and the remnant gel wiped off. The gel can be administered to healthy skin around the lesions, whereas application near the eyes, nostrils, mouth, ears or mucosa should be avoided (keep a distance of 1 cm). Direct contact of Ameluz with the eyes or mucous membrane should be avoided. In case of accidental contact, rinsing with water is recommended.

Illumination: Immediately after cleaning the lesions, the entire treatment area will be illuminated with a red light source. During illumination the lamp should be fixed at the distance from the skin surface that is indicated in the user manual. A narrow spectrum lamp is recommended to achieve higher clearance rates. Symptomatic treatment of transient adverse site reactions may be considered. A broader and continuous spectrum may be used if narrow-spectrum light sources are not tolerated (see sections 4.8 and 5.1). See also section 6.6.

Lesions should be re-assessed after three months, at which point any residual lesions or fields may be retreated. It is recommended that the response of BCC lesions may be confirmed by histological examination of biopsy material, if considered necessary. Subsequently, close long term clinical monitoring of BCC is recommended, with histology if necessary.

4.3 Contraindications

- Hypersensitivity to the active substance, to porphyrins, to soybeans or peanuts, or to any of the excipients listed in section 6.1.
- Porphyria.
- Known photodermatoses of varying pathology and frequency, e.g. metabolic disorders such as aminoaciduria, idiopathic or immunological disorders such as polymorphic light reaction, genetic disorders such as xeroderma pigmentosum, and diseases precipitated or aggravated by exposure to sun light such as lupus erythematoïdes or pemphigus erythemoides.
4.4 Special warnings and precautions for use

Risk of Transient Global Amnesia (TGA)
Photodynamic therapy (PDT) may be a precipitating factor for transient global amnesia in very rare instances. Although the exact mechanism is not known, stress and pain associated with PDT may increase the risk to develop transient amnesia. If amnesia is observed, the PDT must be discontinued immediately (see section 4.8).

Use of immunosuppressants
As inflammatory response is important for the effect of PDT, the trial investigating the efficacy and safety of Ameluz for the treatment of basal cell carcinoma excluded patients who were undergoing treatment with immunosuppression therapy. Therefore, the use of immunosuppressants during treatment with Ameluz is not recommended.

Ameluz should not be used on bleeding lesions
Any bleeding must be stopped before application of the gel. No experience exists for the use of Ameluz in patients with inherited or acquired coagulation defects. Special care should be taken to avoid bleeding during lesion preparation in such patients (see section 4.2).

Risk of mucous membrane and eye irritation
Ameluz can cause mucous membrane or eye irritation. The excipient sodium benzoate may be mildly irritant to the skin, eyes and mucous membranes. Propylene glycol may cause irritation. Special care should be taken to avoid applying Ameluz into eyes or to mucous membranes. In case of accidental contact, the site must be rinsed with water.

Ameluz should not be used on skin areas affected by other diseases or tattoos.
The success and assessment of treatment may be impaired if the treated area is affected by the presence of skin diseases (skin inflammation, located infection, psoriasis, eczema, and malignant skin cancers) as well as tattoos. No experience exists with these situations.

Ameluz transiently increases phototoxicity
Any UV-therapy should be discontinued before treatment. As a general precaution, sun exposure on the treated lesion sites and surrounding skin should be avoided for approximately 48 hours following treatment. Concomitant use of medicinal products with known phototoxic or photoallergic potential such as St. John’s wort, griseofulvin, thiazide diuretics, sulfonylureas, phenothiazines, sulphonamides, quinolones and tetracyclines may enhance the phototoxic reaction to photodynamic therapy.

Risk of allergic reaction
Ameluz contains soybean phosphatidylcholine and should not be applied to patients known to be allergic to peanut or soya (see section 4.3).

4.5 Interaction with other medicinal products and other forms of interaction

Ameluz does not increase 5-aminolaevulinic acid or protoporphyrin IX plasma levels following topical application.
No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of 5-aminolaevulinic acid in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Ameluz during pregnancy.
Breast-feeding
It is unknown whether 5-aminolaevulinic acid/metabolites are excreted in human milk. A risk to the suckling child cannot be excluded. Breast-feeding should be discontinued for 12 hours after treatment with Ameluz.

Fertility
There are no data available on the effect of 5-aminolaevulinic acid on fertility.

4.7 Effects on ability to drive and use machines
Ameluz has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
In clinical trials with Ameluz, local skin reactions at the application site were observed in up to 96% of the subjects treated for actinic keratosis and in all subjects treated for basal cell carcinoma. This is to be expected as the therapeutic principle of photodynamic therapy is based on phototoxic effects of protoporphyrin IX which is synthesized from the active ingredient 5-aminolaevulinic acid.

The most common signs and symptoms are application site irritation, erythema, pain, and oedema. The intensity of these effects is dependent on the type of illumination used for photodynamic therapy. The increased effects correlate with the higher clearance rate of narrow spectrum lamps (see section 5.1). Most adverse reactions occur during illumination or shortly afterwards. The symptoms are usually of mild or moderate intensity (investigator’s assessment on a 4-point scale), and last for 1 to 4 days in most cases; in some cases, however, they may persist for 1 to 2 weeks or even longer. In rare cases, the adverse reactions required interruption or discontinuation of the illumination.

Tabulated list of adverse reactions
The incidence of adverse reactions in 522 subjects exposed to photodynamic therapy with Ameluz in pivotal clinical trials and incidence of adverse reactions reported post-marketing is listed below. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (≥1/10,000), and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: Summary of related adverse drug reactions (ADRs) reported in patients treated with photodynamic therapy with 5-aminolaevulinic acid

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Frequency</th>
<th>Adverse reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Uncommon</td>
<td>At application site: Pustules</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not at application site: Rash pustular</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Uncommon</td>
<td>Nervousness</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Common</td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Dysaesthesia</td>
</tr>
<tr>
<td></td>
<td>Not known*</td>
<td>Transient global amnesia (incl. confusion and disorientation)</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Uncommon</td>
<td>Eyelid oedema, vision blurred, visual impairment</td>
</tr>
<tr>
<td>Skin and subcutaneous disorders</td>
<td>Uncommon</td>
<td>Blister, dry skin, petechiae</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Uncommon</td>
<td>Back pain</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Very common</td>
<td>At application site: Erythema, irritation, pain (incl. burning pain), pruritus, oedema, exfoliation, scab</td>
</tr>
</tbody>
</table>
Common

At application site: Induration, vesicles, paraesthesia, hyperalgesia, erosion, discomfort, discharge

Uncommon

At application site: Haemorrhage, warmth, discoloration, ulcer, swelling, inflammation

Not at application site: Chills, feeling hot, pyrexia, pain, fatigue

| Injury, poisoning and procedural complications | Uncommon | Wound secretion |

* Data from post-marketing period. Four case reports (3 cases from the scientific literature and 1 spontaneous case report) pertaining to the events of this sections. Confusion or disorientation were reported as additional events.

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 **Overdose**

Overdose following topical administration is unlikely and has not been reported in clinical studies. If Ameluz is accidentally ingested, systemic toxicity is unlikely. Protection from sun light exposure for 48 hours and observation are nevertheless recommended.

5. **PHARMAKOLOGICAL PROPERTIES**

5.1 **Pharmacodynamic properties**

Pharmacoherapeutic group: Antineoplastic agents, sensitizers used in photodynamic/radiation therapy, ATC code: L01XD04

**Mechanism of action**

Following topical application of 5-aminolaevulinic acid (ALA), the substance is metabolized to protoporphyrin IX, a photoactive compound which accumulates intracellularly in the treated actinic keratosis and basal cell carcinoma lesions. Protoporphyrin IX is activated by illumination with red light of a suitable wavelength and energy. In the presence of oxygen, reactive oxygen species are formed. The latter causes damage of cellular components and eventually destroys the target cells.

**Clinical efficacy and safety**

*Treatment of actinic keratosis (AK):*

Efficacy and safety of Ameluz for the treatment of actinic keratosis (AK) has been evaluated in 644 patients enrolled in clinical trials. In clinical phase III, a total of 384 patients were treated with Ameluz. All patients had 4 to 8 mild to moderate actinic keratosis lesions on the face and/or scalp. The application site preparation and duration of incubation followed the description under section 4.2. If not completely cleared 12 weeks after initial treatment, lesions or cancerized fields were treated a second time with an identical regimen.

In a randomised, observer blinded clinical trial with 571 AK patients and a follow-up duration of 6 and 12 months, photodynamic therapy with Ameluz was tested for non-inferiority to a commercially registered cream containing 16% methyl-aminolevulinate (MAL, methyl-[5-amino-4-oxopentanoate])
and superiority over placebo. The red light source was either a narrow light spectrum lamp (Aktilite CL 128 or Omniliux PDT) or a lamp with a broader and continuous light spectrum (Waldmann PDT 1200 L, or Hydrosun Photodyn 505 or 750). The primary endpoint was complete patient clearance 12 weeks after the last photodynamic therapy. Ameluz (78.2%) was significantly more effective than MAL (64.2%, [97.5%-confidence interval: 5.9; ∞]) and placebo (17.1%, [95%-confidence interval: 51.2; 71.0]). Total lesion clearance rates were higher for Ameluz (90.4%) compared to MAL (83.2%) and placebo (37.1%). Clearance rates and tolerability were dependent on the illumination source. The following table presents the efficacy and the adverse reactions transient pain and erythema occurring at the application site during photodynamic therapy with different light sources:

Table 2a: Efficacy and adverse reactions (transient pain and erythema) occurring at the application site during photodynamic therapy with different light sources for the treatment of AK

<table>
<thead>
<tr>
<th>Light source</th>
<th>Medicinal product</th>
<th>Total patient clearance (%)</th>
<th>Application site erythema (%)</th>
<th>Application site pain (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Narrow spectrum</td>
<td>Ameluz</td>
<td>85</td>
<td>13</td>
<td>43</td>
</tr>
<tr>
<td>Broad spectrum</td>
<td>Ameluz</td>
<td>72</td>
<td>32</td>
<td>29</td>
</tr>
<tr>
<td>MAL</td>
<td>68</td>
<td>18</td>
<td>43</td>
<td>29</td>
</tr>
</tbody>
</table>

Clinical efficacy was re-assessed at follow-up visits 6 and 12 months after the last photodynamic therapy. Recurrence rates after 12 months were slightly better for Ameluz (41.6%, [95%-confidence interval: 34.4; 49.1]) as compared to MAL (44.8%, [95%-confidence interval: 36.8; 53.0]) and dependent on the light spectrum used for illumination, in favour of narrow spectrum lamps. Prior to the decision to undergo photodynamic therapy it should be taken into consideration that the probability of a subject to be completely cleared 12 months after the last treatment was 53.1% or 47.2% for treatment with Ameluz and 40.8% or 36.3% for MAL treatment with narrow spectrum lamps or all lamp types, respectively. The probability of patients in the Ameluz group to require only 1 treatment and remain completely cleared 12 months after the photodynamic therapy was 32.3%, that of patients in the MAL group 22.4% on average with all lamps.

Cosmetic outcome assessed 12 weeks after the last photodynamic therapy (with baseline sum score 0 excluded) was judged as: very good or good in 43.1% of subjects in the Ameluz group, 45.2% in the MAL group and 36.4% in the placebo group; and unsatisfactory or impaired in 7.9%, 8.1% and 18.2% of subjects, respectively.

Ameluz was also compared with placebo treatment in a randomised, double-blind clinical trial enrolling 122 AK patients. The red light source provided either a narrow spectrum around 630 nm at a light dose of 37 J/cm² (Aktilite CL 128) or a broader and continuous spectrum in the range between 570 and 670 nm at a light dose of 170 J/cm² (Photodyn 750). The primary endpoint was complete patient clearance after 12 weeks following the last photodynamic therapy. Photodynamic therapy with Ameluz (66.3%) was significantly more effective than with placebo (12.5%, p < 0.0001). Total lesion clearance was higher for Ameluz (81.1%) compared to placebo (20.9%). Clearance rates and tolerability were dependent on the illumination source in favour of the narrow spectrum light source. Clinical efficacy was maintained during the follow-up periods of 6 and 12 months after the last photodynamic therapy. Prior to the decision to undergo photodynamic therapy it should be taken into consideration that the probability of a subject to be completely cleared 12 months after the last treatment was 67.5% or 46.8% for treatment with Ameluz with narrow spectrum lamps or all lamp types, respectively. The probability to require only one treatment with Ameluz and remain completely cleared 12 months later was 34.5% on average with all lamps.

Table 2b: Efficacy and adverse reactions (transient pain and erythema) occurring at the application site during photodynamic therapy with different light sources for the treatment of AK

<table>
<thead>
<tr>
<th>Light source</th>
<th>Medicinal product</th>
<th>Total patient clearance (%)</th>
<th>Application site erythema (%)</th>
<th>Application site pain (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Narrow spectrum</td>
<td>Ameluz</td>
<td>85</td>
<td>13</td>
<td>43</td>
</tr>
<tr>
<td>Broad spectrum</td>
<td>Ameluz</td>
<td>72</td>
<td>32</td>
<td>29</td>
</tr>
<tr>
<td>MAL</td>
<td>68</td>
<td>18</td>
<td>43</td>
<td>29</td>
</tr>
</tbody>
</table>
In both AK studies the clearance rates were higher after illumination with narrow light spectrum devices but the incidence and intensity of administration site disorders (e.g. transient pain, erythema) increased in patients illuminated with these devices (see tables above and section 4.8).

The cosmetic outcome was assessed as very good or good in 47.6% of the subjects in the Ameluz group compared to 25.0% of subjects in the placebo group. An unsatisfactory or impaired cosmetic outcome was judged for 3.8% of the subjects in the Ameluz group and in 22.5% of the subjects in the placebo group.

Field cancerization is characterised by an area of skin where multiple AK lesions are present and there is likely to be an underlying and surrounding area of actinic damage (a concept known as field cancerization or field change); the extent of this area may not be evident visually or by physical examination. In a third randomised, double-blind clinical trial, enrolling 87 patients, Ameluz and placebo were compared on entire treatment fields (field cancerization) containing 4 to 8 AK lesions in a field area of maximum 20 cm². The red light source provided a narrow spectrum around 635 nm at a light dose of 37 J/cm² (BF-RhodoLED). Ameluz was superior to vehicle with respect to patient complete clearance rates (90.9% vs. 21.9% for Ameluz and placebo, respectively; p < 0.0001) and lesion complete clearance rates (94.3% vs. 32.9%, respectively; p < 0.0001), as controlled 12 weeks after the last PDT. 96.9 % of patients with AK on the face or forehead were cleared from all lesions, 81.8 % of patients with AK on the scalp were totally cleared. Lesions of mild severity were cleared by 99.1 % vs. 49.2 %, those of moderate severity by 91.7 % vs. 24.1 % for treatment with Ameluz and placebo, respectively. After only 1 PDT complete patient clearance resulted in 61.8 % vs. 9.4 %, and complete lesion clearance in 84.2 % vs. 22.0 % for Ameluz and placebo treatment, respectively.

Clinical efficacy was maintained during the follow-up periods of 6 and 12 months after the last PDT. After Ameluz treatment, 6.2% of the lesions were recurrent after 6 and additionally 2.9% after 12 months, respectively (placebo: 1.9% after 6 and additionally 0% after 12 months, respectively). Patient recurrence rates were 24.5 % and 14.3 % after 6 months, and additionally 12.2 % and 0 % after 12 months for Ameluz and placebo, respectively.

The field treatment applied in this study allowed the assessment of skin quality changes at baseline and 6 and 12 months after the last PDT by severity. The percentage of patients with skin impairment before PDT and 12 months after PDT is listed in the table below. All skin quality parameters in the treated area continuously improved up to the 12-month follow-up time point.

<table>
<thead>
<tr>
<th>Spectrum</th>
<th>Ameluz</th>
<th>87</th>
<th>26</th>
<th>67</th>
<th>7</th>
<th>30</th>
<th>35</th>
<th>16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Narrow</td>
<td>Ameluz</td>
<td>53</td>
<td>47</td>
<td>19</td>
<td>0</td>
<td>35</td>
<td>14</td>
<td>0</td>
</tr>
</tbody>
</table>

In both AK studies the clearance rates were higher after illumination with narrow light spectrum devices but the incidence and intensity of administration site disorders (e.g. transient pain, erythema) increased in patients illuminated with these devices (see tables above and section 4.8).
Table 3: Skin quality parameters in the treated area during 12-month follow-up

<table>
<thead>
<tr>
<th>Type of skin impairment</th>
<th>Severity</th>
<th>AMELUZ Before PDT (%)</th>
<th>12 months after PDT (%)</th>
<th>Vehicle Before PDT (%)</th>
<th>12 months after PDT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Before PDT (%)</td>
<td>12 months after PDT (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roughness/ dryness/ scaliness</td>
<td>None</td>
<td>15</td>
<td>72</td>
<td>11</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>50</td>
<td>26</td>
<td>56</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>Moderate/ severe</td>
<td>35</td>
<td>2</td>
<td>33</td>
<td>8</td>
</tr>
<tr>
<td>Hyper-pigmentation</td>
<td>None</td>
<td>41</td>
<td>76</td>
<td>30</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>52</td>
<td>24</td>
<td>59</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>Moderate/ severe</td>
<td>7</td>
<td>0</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Hypo-pigmentation</td>
<td>None</td>
<td>54</td>
<td>89</td>
<td>52</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>43</td>
<td>11</td>
<td>44</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>Moderate/ severe</td>
<td>4</td>
<td>0</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Mottled or irregular pigmentation</td>
<td>None</td>
<td>52</td>
<td>82</td>
<td>48</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>44</td>
<td>17</td>
<td>41</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Moderate/ severe</td>
<td>4</td>
<td>2</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Scarring</td>
<td>None</td>
<td>74</td>
<td>93</td>
<td>74</td>
<td>89</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>22</td>
<td>7</td>
<td>22</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Moderate/ severe</td>
<td>4</td>
<td>0</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Atrophy</td>
<td>None</td>
<td>69</td>
<td>96</td>
<td>70</td>
<td>92</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>30</td>
<td>4</td>
<td>30</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Moderate/ severe</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Treatment of basal cell carcinoma (BCC):**

Efficacy and safety of Ameluz for the treatment of basal cell carcinoma (BCC) with a thickness of <2mm has been evaluated in 281 patients enrolled in a phase III clinical trial. In this study a total of 138 patients were treated with Ameluz. All patients had 1 to 3 BCC lesions on the face/forehead, bald scalp, extremities and/or neck/trunk. In this study, photodynamic therapy with Ameluz was tested for non-inferiority to a cream containing 16% methyl-aminolevulinate (MAL, methyl-[5-amino-4-oxopentanoate]). The red light source provided a narrow spectrum around 635 nm at a light dose of 37 J/cm² (BF-RhodoLED). The primary endpoint was complete patient clearance 12 weeks after the last photodynamic therapy.

The complete patient clearance rate for Ameluz was 93.4%, compared to 91.8% for the comparator MAL. The study demonstrated the non-inferiority of Ameluz compared to MAL cream [97.5% - confidence interval -6.5]. Of the BCC lesions, 94.6% were cleared with Ameluz, 92.9% with MAL. For nodular BCC, 89.3% of the lesions were cleared with Ameluz, 78.6% with MAL. Adverse events and tolerability were comparable for both treatments.

Clinical efficacy was re-assessed at follow-up visits 6 and 12 months after the last photodynamic therapy. Lesion recurrence rates after 6 and 12 months were 2.9% and 4.3%, respectively, for Ameluz and 6.7% and 8.2% for MAL.
Table 4: Efficacy of PDT for the treatment of BCC for all patients and selected subgroups

<table>
<thead>
<tr>
<th></th>
<th>Ameluz</th>
<th>Ameluz</th>
<th>Ameluz</th>
<th>MAL</th>
<th>MAL</th>
<th>MAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patient number</td>
<td>Full patient clearance</td>
<td>Full lesion clearance</td>
<td>Patient number</td>
<td>Full patient clearance</td>
<td>Full lesion clearance</td>
</tr>
<tr>
<td>Total</td>
<td>121</td>
<td>113 (93.4)</td>
<td>140 (94.6)</td>
<td>110</td>
<td>101 (91.8)</td>
<td>118 (92.9)</td>
</tr>
<tr>
<td><strong>Subgroups:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with more than 1 BCC</td>
<td>23 (19.0)</td>
<td>23/23 (100.0)</td>
<td>n.a.</td>
<td>16 (14.5)</td>
<td>14/16 (87.5)</td>
<td>n.a.</td>
</tr>
<tr>
<td>Superficial (only)</td>
<td>95 (78.5)</td>
<td>90/95 (94.7)</td>
<td>114/119 (95.8)</td>
<td>83 (75.5)</td>
<td>80/83 (96.4)</td>
<td>95/98 (96.9)</td>
</tr>
<tr>
<td>Nodular (only)</td>
<td>21 (17.4)</td>
<td>18/21 (85.7)</td>
<td>25/28 (89.3)</td>
<td>21 (19.1)</td>
<td>16/21 (76.2)</td>
<td>22/28 (78.6)</td>
</tr>
<tr>
<td>Others (including mixed s/nBCCs)</td>
<td>5 (4.1)</td>
<td>5/5 (100.0)</td>
<td>1/1 (100.0)</td>
<td>6 (5.5)</td>
<td>5/6 (83.3)</td>
<td>1/1 (100.0)</td>
</tr>
<tr>
<td>Thickness &gt;1mm</td>
<td>n.a.</td>
<td>n.a.</td>
<td>8/11 (72.7)</td>
<td>n.a.</td>
<td>n.a.</td>
<td>8/12 (66.7)</td>
</tr>
<tr>
<td>BCC on the head (only)</td>
<td>13 (10.7)</td>
<td>10/13 (76.9)</td>
<td>14/17 (82.4)</td>
<td>14 (12.7)</td>
<td>10/14 (71.4)</td>
<td>12/17 (70.6)</td>
</tr>
<tr>
<td>BCC on the trunk (only)</td>
<td>77 (63.6)</td>
<td>75/77 (97.4)</td>
<td>95/97 (97.9)</td>
<td>73 (66.4)</td>
<td>70/73 (95.9)</td>
<td>84/87 (96.6)</td>
</tr>
</tbody>
</table>

Patient distribution in the subgroups was similar for both products and represents the distribution in the general population, where more than 70% of BCCs are located in the head/trunk region. BCCs located in this region mainly belong to the superficial subtype. In conclusion, even though subgroup sizes are too small to draw significant conclusions on individual groups, the distribution of the two products to the relevant subgroups is very similar. Thus, it seems not plausible that this could negatively impact the non-inferiority claim of the primary study endpoint or the general trends observed across all subgroups.

In a clinical trial designed to investigate the sensitization potential of ALA with 216 healthy subjects, 13 subjects (6%) developed allergic contact dermatitis after continuous exposure for 21 days with doses of ALA that were higher than doses normally used in the treatment of AK. Allergic contact dermatitis has not been observed under regular treatment conditions.

Actinic keratosis lesion severity was graded according to the scale described by Olsen et al., 1991 (J Am Acad Dermatol 1991; 24: 738-743):

<table>
<thead>
<tr>
<th>Grade</th>
<th>Clinical description of severity grading</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>none</td>
</tr>
<tr>
<td>1</td>
<td>mild</td>
</tr>
<tr>
<td>2</td>
<td>moderate</td>
</tr>
<tr>
<td>3</td>
<td>severe</td>
</tr>
</tbody>
</table>

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Ameluz in all subsets of the paediatric population in actinic keratosis (see section 4.2 for information on paediatric use).
5.2 Pharmacokinetic properties

Absorption

*In vitro* dermal absorption into human skin was studied using Ameluz containing radiolabelled 5-aminolaevulinic acid (ALA). After 24 hours, the mean cumulative absorption (including accumulation in the dermis) through human skin was 0.2% of the administered dose. Corresponding studies in human skin with actinic keratosis lesions and/or roughened surface were not performed.

Distribution

In a phase II clinical trial, 5-aminolaevulinic acid and protoporphyrin IX serum levels and ALA urine levels were measured before, 3 and 24 hours after administration of Ameluz for photodynamic treatment. None of the post-dose levels were increased in comparison to the naturally occurring pre-dose levels, showing absence of a relevant systemic absorption after topical administration.

A maximal use PK study was conducted in 12 patients bearing at least 10 mild to moderate AKs on the face or forehead. An entire tube of vehicle and Ameluz followed by PDT was applied in a fixed sequence design with a washout period of 7 days to evaluate baseline and Ameluz dependent plasma concentrations of ALA and PpIX. In most patients an up to 2.5-fold increase of basic ALA plasma concentrations was observed during the first 3 hours after Ameluz application, which is still within the normal range of previously reported and published endogenous ALA concentrations. The plasma concentrations of metabolite PpIX were generally low in all patients and in none of the patients, an obvious increase of PpIX plasma concentrations was observed after Ameluz application.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on dermal toxicity studies or studies reported in the literature of repeated dose toxicity, genotoxicity and reproductive toxicity. Carcinogenicity studies have not been performed with ALA.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Xanthan gum
Soybean phosphatidylcholine
Polysorbate 80
Triglycerides, medium-chain
Isopropyl alcohol
Disodium phosphate dihydrate
Sodium dihydrogen phosphate dihydrate
Propylene glycol
Sodium benzoate (E211)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened tube: 18 months
After first opening: 12 weeks
6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Keep the tube tightly closed after first opening.

6.5 Nature and contents of container

One outer carton containing one aluminium tube with epoxyphenol inner lacquer and a latex seal and a screw cap of high density polyethylene. Each tube contains 2 g of gel.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Each lamp should be used according to the user manual. Only CE marked lamps should be used, equipped with the necessary filters and/or reflecting mirrors to minimize exposure to heat, blue light and ultra violet (UV) radiation. The technical specifications of the device need to be checked before using a specific light source, and the requirements must be met for the intended light spectrum. Both the patient and the medical personnel conducting the photodynamic therapy should adhere to any safety instructions provided with the light source used. During illumination, patient and medical personnel should wear suitable protective goggles. There is no need to protect healthy untreated skin surrounding the treated actinic keratosis lesions.

7. MARKETING AUTHORISATION HOLDER

Biofrontera Bioscience GmbH
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51377 Leverkusen
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Tel: +49-214-87632-66
Fax: +49-214-87632-90
Email: ameluz@biofrontera.com

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/740/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 December 2011
Date of latest renewal: 21 November 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.
ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT
A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Biofrontera Pharma GmbH
Hemmelrather Weg 201
D-51377 Leverkusen
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- Risk Management Plan (RMP)

The MAH shall perform the pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency.
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.
ANNEX III

LABELLING AND PACKAGE LEAFLET
A. LABELLING
**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**Outer Carton**

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
</table>
| **Ameluz 78 mg/g gel**  
| 5-aminolaevulinic acid             |

<table>
<thead>
<tr>
<th>2. STATEMENT OF ACTIVE SUBSTANCE(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>One gram contains 78 mg of 5-aminolaevulinic acid (as hydrochloride).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. LIST OF EXCIPIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xanthan gum, soybean phosphatidylcholine, polysorbate 80, triglycerides medium-chain, isopropyl alcohol, disodium phosphate dihydrate, sodium dihydrogen phosphate dihydrate, propylene glycol, sodium benzoate (E211), purified water. See package leaflet for further information.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. PHARMACEUTICAL FORM AND CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 g gel</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. METHOD AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Read the package leaflet before use.</td>
</tr>
<tr>
<td>Cutaneous use.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keep out of the sight and reach of children.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>7. OTHER SPECIAL WARNING(S), IF NECESSARY</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>8. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP</td>
</tr>
<tr>
<td>After first opening: 12 weeks</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>9. SPECIAL STORAGE CONDITIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Store in a refrigerator.</td>
</tr>
<tr>
<td>Keep the tube tightly closed after first opening.</td>
</tr>
</tbody>
</table>

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>10.</strong></td>
<td><strong>SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</strong></td>
</tr>
<tr>
<td><strong>11.</strong></td>
<td><strong>NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</strong></td>
</tr>
<tr>
<td></td>
<td>Biofrontera Bioscience GmbH</td>
</tr>
<tr>
<td></td>
<td>Hemmelrather Weg 201</td>
</tr>
<tr>
<td></td>
<td>51377 Leverkusen</td>
</tr>
<tr>
<td></td>
<td>Germany</td>
</tr>
<tr>
<td><strong>12.</strong></td>
<td><strong>MARKETING AUTHORISATION NUMBER(S)</strong></td>
</tr>
<tr>
<td></td>
<td>EU/1/11/740/001</td>
</tr>
<tr>
<td><strong>13.</strong></td>
<td><strong>BATCH NUMBER</strong></td>
</tr>
<tr>
<td></td>
<td>Lot</td>
</tr>
<tr>
<td><strong>14.</strong></td>
<td><strong>GENERAL CLASSIFICATION FOR SUPPLY</strong></td>
</tr>
<tr>
<td><strong>15.</strong></td>
<td><strong>INSTRUCTIONS ON USE</strong></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>16.</strong></td>
<td><strong>INFORMATION IN BRAILLE</strong></td>
</tr>
<tr>
<td></td>
<td>Justification for not including Braille accepted</td>
</tr>
<tr>
<td><strong>17.</strong></td>
<td><strong>UNIQUE IDENTIFIER – 2D BARCODE</strong></td>
</tr>
<tr>
<td></td>
<td>2D barcode carrying the unique identifier not yet available.</td>
</tr>
<tr>
<td><strong>18.</strong></td>
<td><strong>UNIQUE IDENTIFIER - HUMAN READABLE DATA</strong></td>
</tr>
<tr>
<td></td>
<td>PC: {number} [product code]</td>
</tr>
<tr>
<td></td>
<td>SN: {number} [serial number]</td>
</tr>
<tr>
<td></td>
<td>NN: {number} [national reimbursement number or other national number identifying the medicinal product]</td>
</tr>
<tr>
<td></td>
<td>Numbers are not yet assigned/available</td>
</tr>
</tbody>
</table>
**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**Tube**

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ameluz 78 mg/g gel</td>
</tr>
<tr>
<td>5-aminolaevulinic acid</td>
</tr>
<tr>
<td>Cutaneous use</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. METHOD OF ADMINISTRATION</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>3. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. BATCH NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lot</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 g</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. OTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Store in a refrigerator.</td>
</tr>
</tbody>
</table>
B. PACKAGE LEAFLET
Package leaflet: information for the user

Ameluz 78 mg/g gel
5-aminolaevulinic acid

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
• Keep this leaflet. You may need to read it again.
• If you have any further questions, ask your doctor or pharmacist.
• This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
• If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet
1. What Ameluz is and what it is used for
2. What you need to know before you use Ameluz
3. How to use Ameluz
4. Possible side effects
5. How to store Ameluz
6. Contents of the pack and other information

1. What Ameluz is and what it is used for

Ameluz contains the active substance 5-aminolaevulinic acid. It is used to treat:
• slightly palpable to moderately thick actinic keratoses on the face and scalp or entire fields affected by actinic keratoses in adults. Actinic keratoses are certain changes in the outer layer of the skin that can lead to skin cancer.
• superficial and/or nodular basal cell carcinoma unsuitable for surgical treatment due to possible treatment-related morbidity and/or poor cosmetic outcome in adults. Basal cell carcinoma is a skin cancer that can cause reddish, scaly patches or one or several small bumps that bleed easily and do not heal.

After application, the active substance of Ameluz becomes a photoactive substance which accumulates in affected cells. Illumination with appropriate red light produces reactive oxygen-containing molecules which act against the target cells.

2. What you need to know before you use Ameluz

Do not use Ameluz:
• if you are allergic to
  − 5-aminolaevulinic acid or any of the other ingredients of this medicine (listed in section 6)
  − photoactive substances known as porphyrins
  − soybean oil or peanuts
• if you have impaired formation of red blood pigment called porphyria
• if you have other skin conditions caused by or made worse by exposure to light

Warnings and precautions
• In very rare cases photodynamic therapy may increase the risk to develop temporary amnesia.
• Avoid applying Ameluz
  o to bleeding lesions.
  o into eyes or to mucous membranes.
• Discontinue any UV-therapy before treatment.
• Avoid sun exposure on the treated lesion sites and surrounding skin for approximately 48 hours following treatment.
• Do not use Ameluz on skin areas affected by other diseases or tattoos because this may hinder the success and assessment of the treatment.

Children and adolescents
Actinic keratoses do not occur in children and adolescents.

Other medicines and Ameluz
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

Inform your doctor if you use medicines that increase allergic or other harmful reactions after light exposure, such as
• St. John’s wort or its preparations: medicines to treat depression
• griseofulvin: a medicine to treat fungal infections
• medicines to increase water output through your kidneys with active substance names mostly ending in “thiazide” or “tizide” such as hydrochlorothiazide
• certain medicines to treat diabetes, such as glibenclamide, glimepiride
• medicines to treat mental disorders, nausea or vomiting with active substance names mostly ending in “azine” such as phenothiazine
• medicines to treat bacterial infection with active substance names beginning with “sulfa” or ending in “oxacin” or “cycline” such as tetracycline

Pregnancy, breast-feeding and fertility
As a precautionary measure, avoid the use of Ameluz during pregnancy, due to no or limited data. Breast-feeding should be discontinued for 12 hours after treatment with Ameluz. There are no data available on the effect of 5-aminolaevulinc acid on fertility.

Driving and using machines
Ameluz has no or negligible influence on the ability to drive and use machines.

Ameluz contains:
• sodium benzoate: Mildly irritant to the skin, eyes and mucous membranes.
• soybean phosphatidylcholine: If you are allergic to peanut or soya, do not use this medicine.
• propylene glycol: May cause skin irritation.

3. How to use Ameluz
Ameluz is only administered under the supervision of health care professionals. A therapy session can be administered for single or multiple lesions or entire treatment fields.

Usual dose
Ameluz is applied to form a film of about 1 mm thickness to the entire lesions or fields and approximately 5 mm of the surrounding area using glove protected fingertips or a spatula.

Before use
The application area is first wiped with an ethanol or isopropanol-soaked cotton pad to degrease the skin. Scales and crusts are then carefully removed and all lesion surfaces are gently roughened. Care is taken to avoid bleeding.

Method of administration
Ameluz is only used on the skin (cutaneous use). Avoid any contact with the eyes, nostrils, mouth, ears, mucous membrane or bleeding lesions. A distance of at least 1 cm is to be maintained. Rinse with water if such contact occurs.

The gel is allowed to dry for approximately 10 minutes before placing a light-tight dressing over the treatment site. The dressing is removed after 3 hours. The remaining gel is wiped off.
After cleaning
Immediately after cleaning, the entire treated area is illuminated using a red light source. Efficacy and side effects such as temporary pain are dependent on the light source used.

Both patients and healthcare professionals should adhere to any safety instructions provided with the light source used during therapy. All should wear suitable protective goggles during illumination. There is no need to protect healthy untreated skin.

Duration of use

- For treatment of actinic keratosis:
  One PDT session should be provided. The treated lesions should be evaluated 3 months after treatment. If actinic keratosis is still present it should be re-treated in a second session.

- For treatment of basal cell carcinoma:
  Two sessions should be provided with an interval of one week between sessions. The treated lesions should be evaluated 3 months after treatment. If basal cell carcinoma lesions are still present, the treatment should be repeated.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Side effects at the place where the gel is applied occur in about 9 of 10 users and indicate that the affected cells respond to the treatment.

Usually, side effects are of mild or moderate intensity, and may typically occur during illumination or after 1 to 4 days. However, in some cases they may persist for 1 to 2 weeks or even longer. In rare cases, interruption or discontinuation of illumination may be necessary. After more extended time periods, treatment with Ameluz frequently results in continued improvement of skin quality parameters.

Side effects can occur with the following frequencies:

**Very common:** may affect more than 1 in 10 people
- reactions at the application site
  - skin reddening
  - irritation
  - pain (incl. burning)
  - itching
  - tissue swelling caused by excess fluid
  - scaling of the skin
  - scab

**Common:** may affect up to 1 in 10 people
- reactions at the application site
  - hardening
  - vesicles
  - abnormal sensation, such as pricking, tingling or numbness
  - increased sensitivity to pain
  - abrasion
  - discomfort
  - discharge
  - headache
**Uncommon:** may affect up to 1 in 100 people
- reactions at the application site
  - bleeding
  - warmth
  - change of colour
  - swelling
  - ulcer
  - red or purple spots on the body
  - pustules
  - inflammation
- blister
- dry skin
- eyelid swelling caused by excess fluid, blurred vision or visual impairment
- unpleasant, abnormal sense of touch
- chills
- feeling hot, fever
- pain
- nervousness
- wound secretion
- fatigue

**Not known:** data from post-marketing
- temporary amnesia
- increased blood pressure
- eye irritation

**Reporting of side effects:**

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

**5. How to store Ameluz**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the tube and carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C).

Keep the tube tightly closed after first opening. Discard open tubes 12 weeks after opening.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

**6. Contents of the pack and other information**

**What Ameluz contains**
- The active substance is 5-aminolaevulinic acid.
  1 g Ameluz contains 78 mg of 5-aminolaevulinic acid (as hydrochloride).
- The other ingredients are:
  disodium phosphate dihydrate, isopropyl alcohol, polysorbate 80, propylene glycol, purified
water, sodium benzoate (E211), sodium dihydrogen phosphate dihydrate, soybean phosphatidylcholine, triglycerides medium-chain, xanthan gum. See section 2.

What Ameluz looks like and contents of the pack
Ameluz is a white to yellowish gel.
Each carton contains one aluminium tube with 2 g gel closed with a polyethylene screw cap.

Marketing Authorisation Holder
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Tel: +49 214 87632 66, Fax: +49 214 87632 90
Email: ameluz@biofrontera.com

Manufacturer
Biofrontera Pharma GmbH
Hemmelrather Weg 201
51377 Leverkusen, Germany
Tel: +49 214 87632 66, Fax: +49 214 87632 90
Email: ameluz@biofrontera.com

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Biofrontera Pharma GmbH, Германия / Немецко / Deutschland / Saksamaa / Ελλάδα / Hrvatska / Germany / Újváros / Germany / Vācija / Vokietija / Németország / Il-Ġermanja / Niemcy / Alemanha / Nemecko,
Tel. / Tel / Tηλ. / Simi / Tel.: +49 214 87632 66, ameluz@biofrontera.com

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NO Desitin Pharma AS, Norge, Tlf: +47 671592 30, firmapost@desitin.no
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FI Biofrontera Pharma GmbH, Saksan/Tyskland, Puh/Tel: 0800 917631, ameluz-fi@biofrontera.com
SE Desitin Pharma AB, Danmark, Tel: +45 33730073, desitin@desitin.dk

This leaflet was last revised in
Detailed information on this medicine is available on the European Medicines Agency web site: