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RESEARCH**

APPLICATION NUMBER:

208081Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AMELUZ safely and effectively. See full prescribing information for AMELUZ.

AMELUZ® (aminolevulinic acid hydrochloride) gel, 10%, for topical use

Initial U.S. approval: 1999

INDICATIONS AND USAGE

AMELUZ gel, a porphyrin precursor, in combination with photodynamic therapy using BF-RhodoLED lamp, is indicated for the lesion-directed and field-directed treatment of actinic keratoses of mild-to-moderate severity on the face and scalp (1).

DOSAGE AND ADMINISTRATION

- Administer AMELUZ only by a health care provider (2.1).
- AMELUZ is for topical use only (2.1).
- Photodynamic therapy with AMELUZ involves preparation of lesions, application of the product, occlusion and illumination with BF-RhodoLED (2.2).
- Retreat lesions that have not completely resolved 3 months after the initial treatment (2.2).
- See BF-RhodoLED user manual for detailed lamp safety and operating instructions (2).

DOSAGE FORMS AND STRENGTHS

Gel: 10% (3).

CONTRAINDICATIONS

- Known hypersensitivity to porphyrins (4).
- Known hypersensitivity to any component of AMELUZ, which includes soybean phosphatidylcholine (4).
- Porphyria (4).
- Photodermatoses (4).

WARNINGS AND PRECAUTIONS

- *Risk of Eye Injury:* Patients and healthcare providers must wear protective eyewear before operating BF-RhodoLED lamp (5.1).
- *Photosensitivity:* Protect treated lesions from sunlight exposure for 48 hours post treatment (5.2).
- *Risk of Bleeding:* Special care should be taken to avoid bleeding during lesion preparation in patients with inherited or acquired coagulation disorders (5.3).
- *Ophthalmic Adverse Reactions:* Avoid direct contact of AMELUZ with the eyes (5.4).
- *Mucous Membranes Irritation:* Avoid direct contact of AMELUZ with the mucous membranes (5.5).

ADVERSE REACTIONS

Most common adverse reactions ($\geq 10\%$) were application site erythema, pain/burning, irritation, edema, pruritus, exfoliation, scab, induration, and vesicles (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Biofrontera Inc. at 1-884-829-7434 or FDA at 1-800-332-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Concomitant use of the following medications may enhance the phototoxic reaction to photodynamic therapy: St. John's wort, griseofulvin, thiazide diuretics, sulfonylureas, phenothiazines, sulphonamides, quinolones, and tetracyclines (7).

See 17 for PATIENT COUNSELING INFORMATION

Revised: 05/2016

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FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

AMELUZ[®] gel, in combination with photodynamic therapy (PDT) using BF-RhodoLED[®] lamp, a narrowband, red light illumination source, is indicated for lesion-directed and field-directed treatment of actinic keratoses (AKs) of mild-to-moderate severity on the face and scalp.

2. DOSAGE AND ADMINISTRATION

2.1 Important Administration Information

AMELUZ, in conjunction with lesion preparation, is only to be administered by a health care provider.

AMELUZ is for topical use only. Not for ophthalmic, oral, or intravaginal use.

Treat single lesions or an entire field affected by multiple lesions with AMELUZ, in combination with red light photodynamic therapy (PDT). PDT requires administration of both AMELUZ and BF-RhodoLED light. Retreat lesions that have not completely resolved after 3 months after the initial treatment.

Refer to BF-RhodoLED user manual for detailed lamp safety and operating instructions. Both patient and medical personnel conducting the PDT should adhere to all safety instructions.

2.2 Dosage and Administration Instructions

PDT is a multi-stage process:

Step 1. Preparation of Lesions

Before applying AMELUZ, carefully wipe all lesions with an ethanol or isopropanol-soaked cotton pad to ensure degreasing of the skin.



Figure 1A: Degreasing the skin

Thereafter, remove any scaling and crusts and gently roughen all lesion surfaces, taking care to avoid bleeding.



Figure 1B: Removal of scales and crust

Step 2. Application of AMELUZ

Use glove protected fingertips or a spatula to apply AMELUZ. Apply gel approximately 1 mm thick and include approximately 5 mm of the surrounding skin. Use sufficient amount of gel to cover the single lesions or if multiple lesions, the entire area. Application area should not exceed 20 cm² and no more than 2 grams of AMELUZ (one tube) should be used at one time. The gel can be applied to healthy skin around the lesions. Avoid application near mucous membranes such as the eyes, nostrils, mouth, and ears (keep a distance of 1 cm from these areas). In case of accidental contact with these areas, thoroughly rinse with water. Allow the gel to dry for approximately 10 minutes before applying occlusive dressing.



Figure 2: Drug application

Step 3. Occlusion for 3 Hours

Cover the area where the gel has been applied with a light-blocking, occlusive dressing. Following 3 hours of occlusion, remove the dressing and wipe off any remaining gel.



Figure 3: Occlusion

Step 4. Illumination with Red Light

During illumination, patient and medical personnel need to wear suitable protective eyewear.

Immediately after removing occlusion and any remaining gel, illuminate the treatment area with BF-RhodoLED[®], a red light source with a narrow spectrum around 635 nm that delivers a light dose of approximately 37 J/cm² within 10 minutes. Calibration by the operator is not needed; the illumination time is calculated automatically. Position the lamp head 5-8 cm from the skin's surface. When an area of 8 x 18 cm is illuminated, the effective treatment area is 6 x 16 cm. Larger areas can be illuminated in several steps.

Healthy untreated skin surrounding the AK lesions does not need protection during illumination.

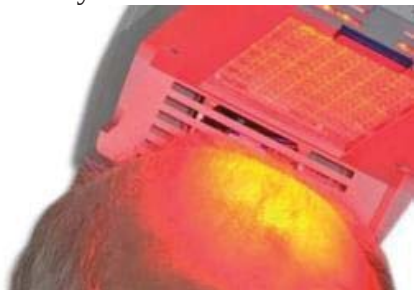


Figure 4: Illumination

If for any reason, the lesions cannot be illuminated within 3 hours after AMELUZ application, rinse off the gel with saline and water. For 2 days, protect the lesion sites and surrounding skin from sunlight or prolonged or intense light (e.g., tanning beds, sun lamps).

3. DOSAGE FORMS AND STRENGTHS

Each gram of AMELUZ gel, 10% contains 100 mg of aminolevulinic acid hydrochloride (equivalent to 78 mg of aminolevulinic acid).

4. CONTRAINDICATIONS

AMELUZ is contraindicated in patients with:

- Known hypersensitivity to porphyrins.
- Known hypersensitivity to any of the components of AMELUZ, which includes soybean phosphatidylcholine.
- Porphyria. AMELUZ use may cause uncontrolled phototoxic effects [see *Warnings and Precautions* (5.2)].
- Photodermatoses. PDT may worsen the phototoxic or photoallergic reactions [see *Warnings and Precautions* (5.2)].

5. WARNINGS AND PRECAUTIONS

5.1 Risk of BF-RhodoLED Lamp Induced Eye Injury

BF-RhodoLED lamp may cause eye irritation, glare, or injury. Before operating the lamp, personnel must refer to the user manual for specific warnings, cautions, and instructions. Eye exposure to the BF-RhodoLED light must be prevented. Protective eye equipment must be used by patient, healthcare providers and any person present during the illumination period. Avoid staring directly into the light source [see *Dosage and Administration* (2)].

5.2 Increased Photosensitivity

AMELUZ increases photosensitivity. Avoid sunlight, prolonged or intense light (e.g., tanning beds, sun lamps) on lesions and surrounding skin treated with AMELUZ for approximately 48 hours following treatment whether exposed to illumination or not. Concomitant use of AMELUZ

with other known photosensitizing agents may increase the risk of phototoxic reaction to PDT [see *Drug Interactions* (7)].

5.3 Risk of Bleeding in Patients with Coagulation Disorders

AMELUZ has not been tested on patients with inherited or acquired coagulation disorders. Special care should be taken to avoid bleeding during lesion preparation in such patients [see *Dosage and Administration* (2)]. Any bleeding must be stopped before application of the gel.

5.4 Ophthalmic Adverse Reactions

Eyelid edema has occurred with AMELUZ application. AMELUZ can cause ophthalmic adverse reactions. AMELUZ is intended for topical use only. Do not apply AMELUZ into the eyes. Rinse eyes with water in case of accidental contact.

5.5 Risk of Mucous Membrane Irritation

AMELUZ can cause mucous membrane irritation. AMELUZ is intended for topical use only. Do not apply AMELUZ to the mucous membranes. Rinse with water in case of accidental contact.

6. ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Risk of BF-RhodoLED Lamp Induced Eye Injury [see *Warnings and Precautions* (5.1)].
- Increased Photosensitivity [see *Warnings and Precautions* (5.2)].
- Risk of Bleeding in Patients with Coagulation Disorders [see *Warnings and Precautions* (5.3)].
- Ophthalmic Adverse Reactions [see *Warnings and Precautions* (5.4)].
- Risk of Mucous Membranes Irritation [see *Warnings and Precautions* (5.5)].

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The clinical program for AMELUZ included three double-blind and placebo-controlled trials (Trials 1, 2, and 3), enrolling a total of 299 subjects that were treated with narrow band light. Trial subjects were adults greater than or equal to 49 years of age, and the majority had Fitzpatrick skin type I, II, or III. No subjects had Fitzpatrick skin type V or VI. Approximately 86% of subjects were male, and all subjects were Caucasian.

For all trials, the enrolled subjects had mild to moderate AKs (Olsen grade 1 and 2) with 4 to 8 lesions on the face and scalp. Overall, 87 placebo-treated subjects (n=16, n=32, n=39) and 212 AMELUZ-treated subjects (n=32, n=55, and n=125) were illuminated with BF-RhodoLED or similar narrow spectrum lamps.

Local skin reactions at the application site were observed in about 99.5% of subjects treated with AMELUZ and narrow spectrum lamps. The most frequent adverse reactions during and after PDT were application site erythema, pain, burning, irritation, edema, pruritus, exfoliation, scab, induration, and vesicles.

Most adverse reactions occurred during illumination or shortly afterwards, were generally of mild or moderate intensity, and lasted for 1 to 4 days in most cases; in some cases, however, they persisted for 1 to 2 weeks or even longer. Severe pain/burning occurred in up to 30% of subjects. In one case, the adverse reactions required interruption or discontinuation of the illumination.

The incidence of common ($\geq 1\%$, $< 10\%$) and very common ($\geq 10\%$) adverse reactions in randomized, multicenter trials at the application site are presented in Table 1.

Table 1: Incidence of Adverse Reactions Occurring at $\geq 1\%$ of the AMELUZ Group and More Frequently than the Vehicle Group in the Actinic Keratosis Trials at the Application Site

Adverse reaction	Vehicle n=87	AMELUZ n=212
Adverse reactions at the application site		
Erythema	34 (39%)	195 (92%)
Pain/Burning	26 (30%)	195 (92%)
Irritation	17 (20%)	153 (72%)
Edema	3 (3%)	75 (35%)
Pruritus	14 (16%)	72 (34%)
Exfoliation	4 (5%)	41 (19%)
Scab	2 (2%)	41 (19%)
Induration	0 (0%)	26 (12%)
Vesicles	1 (1%)	25 (12%)
Paresthesia	2 (2%)	18 (9%)
Hyperalgesia	0 (0%)	10 (5%)
Reaction	2 (2%)	8 (4%)
Discomfort	0 (0%)	7 (3%)
Erosion	0 (0%)	6 (3%)
Discharge	0 (0%)	4 (2%)
Bleeding	0 (0%)	3 (1%)
Pustules	0 (0%)	3 (1%)

Common ($\geq 1\%$, $< 10\%$) adverse reactions not limited to the application site were chills, headache, and skin exfoliation.

Uncommon ($\geq 0.1\%$, $< 1\%$) adverse reactions at the application site for AMELUZ were hemorrhage and swelling. The adverse reactions not limited to the application site were eyelid edema, feeling hot, pain, pyrexia, ulcer, hyperalgesia, rash pustular, nervousness, blister, petechiae, pruritus, scab and skin erosion.

In a clinical trial designed to investigate the sensitization potential of aminolevulinic acid with 216 healthy subjects, 13 subjects (6%) developed allergic contact dermatitis after continuous exposure for 21 days with doses of aminolevulinic acid that were higher than doses normally used in the treatment of AK.

6.2 Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been reported during post-approval use of AMELUZ outside the United States. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Skin and subcutaneous tissue disorders: erythema, swelling, application site inflammation and skin discoloration.

Eye disorders: eye irritation, diplopia, ocular hyperemia, photophobia, and blurred vision.

7. DRUG INTERACTIONS

There have been no formal studies of the interaction of AMELUZ with other drugs. It is possible that concomitant use of other known photosensitizing agents such as St. John's wort, griseofulvin, thiazide diuretics, sulfonamides, phenothiazines, sulphonamides, quinolones and tetracyclines may enhance the phototoxic reaction to PDT [see *Warnings and Precautions (5.1)*].

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on AMELUZ use in pregnant women to inform a drug associated risk. Animal reproduction studies were not conducted with aminolevulinic acid. Systemic absorption of aminolevulinic acid in humans is negligible following topical administration of AMELUZ under maximal clinical use conditions [see *Clinical Pharmacology (12.3)*]. It is not expected that maternal use of AMELUZ will result in fetal exposure to the drug.

The estimated background risk of major birth defects and miscarriage for the indicated population are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

8.2 Lactation

Risk Summary

No data are available regarding the presence of aminolevulinic acid in human milk, the effects of aminolevulinic acid on the breastfed infant or on milk production. However, breastfeeding is not expected to result in exposure of the child to the drug due to the negligible systemic absorption of aminolevulinic acid in humans following topical administration of AMELUZ under maximal clinical use conditions [see *Clinical Pharmacology (12.3)*]. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for AMELUZ and any potential adverse effects on the breastfeeding child from AMELUZ or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients below the age of 18 have not been established. AK is not a condition generally seen in the pediatric population.

8.5 Geriatric Use

Of the 384 subjects exposed to AMELUZ in randomized, multicenter clinical trials, 83% (318/384) of the subjects were 65 years old and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

10. OVERDOSAGE

10.1 AMELUZ Overdose

AMELUZ overdose following topical administration has not been reported. If AMELUZ is accidentally ingested, monitoring and supportive care is recommended. The patient should be advised to avoid incidental sunlight exposure for 48 hours after ingestion.

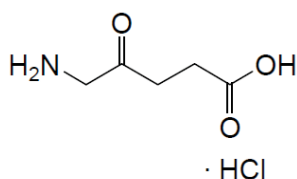
10.2 Red Light Overdose following AMELUZ Administration

There is no information on overdose of red light from the BF-RhodoLED following AMELUZ application.

11. DESCRIPTION

AMELUZ (aminolevulinic acid hydrochloride) gel, 10% for topical use is a non-sterile white-to-yellowish gel. The gel formulation contains a nanoemulsion.

Aminolevulinic acid, a porphyrin precursor, is a white to off-white crystalline solid. It is readily soluble in water, methanol, and dimethylformamide. Its chemical name is 5-amino-4-oxopentanoic acid hydrochloride, molecular weight is 167.59 and molecular formula is $C_5H_9NO_3 \cdot HCl$. The structural formula of aminolevulinic acid hydrochloride is represented below:



Each gram of AMELUZ contains 100 mg of aminolevulinic acid hydrochloride (equivalent to 78 mg aminolevulinic acid) as the active ingredient and the following inactive ingredients: xanthan gum, soybean phosphatidylcholine, polysorbate 80, medium-chain triglycerides, isopropyl alcohol, dibasic sodium phosphate, monobasic sodium phosphate, propylene glycol, sodium benzoate and purified water.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Photoactivation following topical application of AMELUZ occurs when aminolevulinic acid (prodrug) is metabolized to protoporphyrin IX (PpIX), a photoactive compound which accumulates in the skin. When exposed to red light of a suitable wavelength and energy, PpIX is activated resulting in an excited state of porphyrin molecules. In the presence of oxygen, reactive oxygen species are formed which causes damage to cellular components, and eventually destroys the cells. AMELUZ photodynamic therapy of AK lesions utilizes photoactivation of topically applied AMELUZ resulting from BF-RhodoLED illumination, which provides a red light of narrow spectrum and a light dose of approximately 37 J/cm².

12.3 Pharmacokinetics

Pharmacokinetics (PK) of aminolevulinic acid and PpIX was evaluated in a trial of 12 adult subjects with mild to moderate AK with at least 10 AK lesions on the face or forehead. A single dose of one entire tube of AMELUZ (2 grams) was applied under occlusion for 3 hours followed by PDT to a total area of 20 cm². The mean $\pm$ SD baseline plasma aminolevulinic acid and PpIX concentrations were 20.16 $\pm$ 16.53 ng/mL and 3.27 $\pm$ 2.40 ng/mL, respectively. In most subjects, an up to 2.5-fold increase of aminolevulinic acid plasma concentrations was observed during the first 3 hours after AMELUZ application. The mean $\pm$ SD area under the concentration time curve (AUC_{0-t}) and maximum concentration (C_{max}) for baseline corrected aminolevulinic acid (n=12) were 142.83 $\pm$ 75.50 ng.h/mL and 27.19 $\pm$ 20.02 ng/mL, respectively. The median Tmax (time at which C_{max} occurred) was 3 hours.

The majority (about 55%) of the PpIX concentrations were below the limit of quantification (LOQ = 1 ng/mL) and baseline corrected values were negative in all subjects except for one. The baseline corrected AUC_{0-t} and C_{max} in the single subject was 0.07 ng.h/mL and 0.29 ng/mL, respectively. PK of aminolevulinic acid and PpIX following treatment on the scalp was not evaluated.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies to evaluate the carcinogenic potential of AMELUZ or aminolevulinic acid have not been performed.

Aminolevulinic acid revealed no evidence of mutagenic or clastogenic potential based on the results of three in vitro genotoxicity tests (Ames assay, HPRT test in V79 cells, and Human lymphocyte chromosomal aberration assay) and one in vivo genotoxicity test (mouse micronucleus assay). These genotoxicity studies were conducted without exposure to light. There is a literature report that indicates that aminolevulinic acid may cause genotoxic effects in the presence and in the absence of activating light. These genotoxic effects are likely caused by the formation of reactive oxygen species.

Animal fertility studies have not been conducted with aminolevulinic acid because of the negligible systemic absorption of aminolevulinic acid in humans following topical administration of AMELUZ under maximal clinical use conditions.

14. CLINICAL STUDIES

The efficacy and safety of AMELUZ in combination with PDT using a narrow spectrum (red light lamp) source were evaluated in three randomized, multicenter trials (Trials 1, 2, and 3). Trials 2 and 3 were vehicle-controlled and double-blind. Trial 1 was double-blind with respect to vehicle and observer-blind regarding the active comparator arm. All clinical trials included a follow-up assessment after 6 and 12 months.

In these trials, 212 subjects with 4 to 8 mild to moderate AK lesions on the face/forehead and/or bald scalp were treated with AMELUZ and a narrow band spectrum lamp. Subjects ranged from 49 to 87 years of age (mean 71 years), and 92% had Fitzpatrick skin type I, II, or III. No subjects had Fitzpatrick skin type V or VI. Approximately 86% of subjects were male, and all subjects were Caucasian.

All sessions were comprised of lesion preparation to roughen the surface and remove crusts, application of AMELUZ with occlusion for 3 hours, and removal of the residual gel. Subsequently, the entire treatment area was illuminated with a narrow spectrum red light source, a lamp of either 630 nm or 633 nm and a light dose of approximately 37 J/cm². In Trial 3, illumination was performed with BF-RhodoLED, a red light source with a narrow spectrum around 635 nm and a light dose of approximately 37 J/cm².

In all trials, the lesions that were not completely cleared 12 weeks after the initial treatment were treated a second time with an identical regimen. In the trials, 42% (88/212) of subjects needed a second treatment.

The primary endpoint for all trials was complete clearance 12 weeks after the last PDT. The results of Trials 1, 2 and 3 are presented in Table 2.

Table 2: Complete Clearance 12 Weeks After the Last Narrow Spectrum PDT in Subjects with Actinic Keratoses

	Narrow Spectrum PDT	
	AMELUZ	Vehicle
Trial 1	106/125 (85%)	5/39 (13%)
Trial 2	27/32 (84%)	2/16 (13%)
Trial 3	50/55 (91%)	7/32 (22%)

Subjects who achieved complete clearance at 12 weeks after the last PDT entered a 12-month follow-up period. In the three trials, subjects who received AMELUZ with the narrowband PDT and achieved complete clearance 12 weeks after the last PDT had recurrence rates of 14%, 11%, and 25%, respectively (at 6 months) and 40%, 22%, and 37%, respectively (at 12 months). Recurrence was defined as the percentage of subjects with at least one recurrent lesion during the 6-month or 12-month follow-up period in subjects with completely cleared lesions 12 weeks after the last PDT.

In a clinical trial designed to investigate the sensitization potential of aminolevulinic acid hydrochloride with 216 healthy subjects, 13 subjects (6%) developed allergic contact dermatitis after continuous exposure for 21 days with doses of aminolevulinic acid hydrochloride that were higher than doses normally used in the treatment of AK.

16. HOW SUPPLIED/STORAGE AND HANDLING

AMELUZ (aminolevulinic acid hydrochloride) gel, 10% is a white-to-yellowish gel. The drug product is supplied in an aluminum tube with a white, high density polyethylene (HDPE) screw cap. Each tube contains 2 g of gel.

NDC 70621-101-01 2 g tube

Store AMELUZ in a refrigerator, 2°C– 8°C (36°F - 46°F). Excursions permitted to 15°C – 30°C (59°F -86°F).

After opening, AMELUZ can be stored for up to 12 weeks in a refrigerator at 2°C – 8°C (36°F - 46°F) if the tube is tightly closed.

17. PATIENT COUNSELING INFORMATION

17.1 Photosensitivity

Advise patients that for approximately 48 hours following treatment to avoid exposure to sunlight, and prolonged or intense light on the treated lesion sites and surrounding skin.

Advise patients to avoid certain medications that may enhance the phototoxic reaction to PDT [*see Warnings and Precautions (5) and Drug Interactions (7)*].

17.2 Common Adverse Reactions

Inform patients that treatment with AMELUZ in combination with PDT may result in adverse reactions which include local skin reactions at the application site such as erythema, pain/burning, irritation, edema, pruritus, exfoliation, induration, scab, and vesicles.

AMELUZ and BF-RhodoLED are registered trade marks of Biofrontera Pharma GmbH.

PATENT INFO

US patent 6,559,183 and pending patent application US 2009/0324727

Distributed by:

Biofrontera Inc.

201 Edgewater Dr.

Wakefield, MA 01880

USA

Immediate packaging USA

2 ml aluminum tube
revised mock-up for US market authorization
14/04/2016

Background
 White



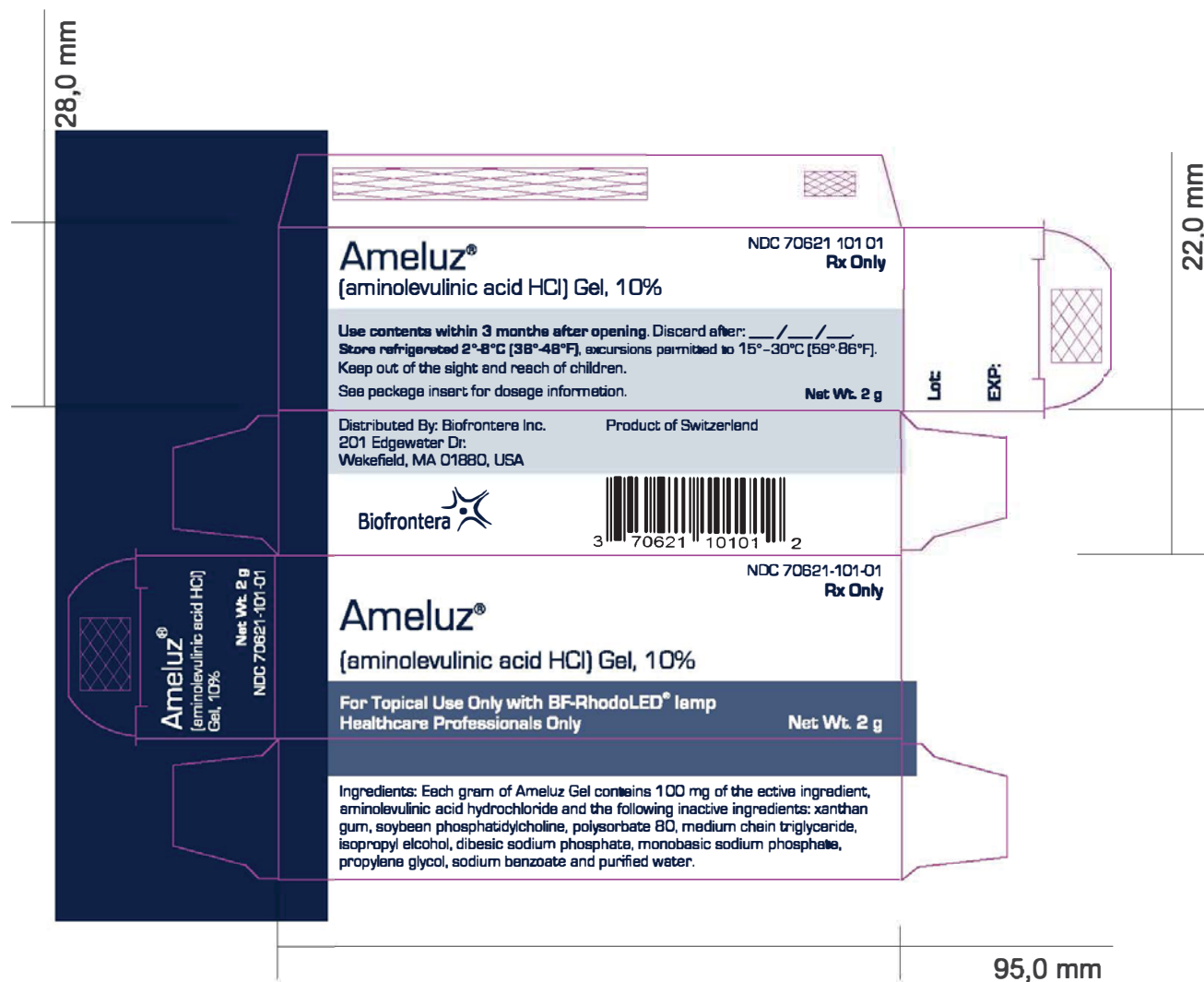
 Area reserved for internal use (i.e. code, article number, etc.)

Labelling outer packaging

5ml outer package

revised mock-up for US market authorization

28.04.2016



Colours:



Black

Outline



Area reserved for internal use (i.e. code, article number, etc.)

BF-RhodoLED®

User Manual



BF-RhodoLED® (US model)

Manufacturer: Biofrontera Pharma GmbH
Distributor: Biofrontera Inc.

Foreword

Thank you for choosing BF-RhodoLED® LED lamp for your photodynamic therapy. BF-RhodoLED® has been developed in accordance with applicable technical standards to provide high energy efficiency as well as constant light emission at the desired wavelength.

Your lamp must be installed and maintained by a certified Biofrontera technician and used only in accordance with the instructions in this manual. You may request the latest printed version covering this model from Biofrontera at any time.

Our drug Ameluz® and medical device BF-RhodoLED® have been approved in combination for photodynamic therapy; the only approved use of our lamp is in combination with Ameluz® gel. This user manual provides important BF-RhodoLED® product details, cautions and warnings, and operating instructions. For Ameluz®, please use its USPI. The Ameluz® prescribing information includes information on how to use the gel along with contraindications, warnings and precautions and dosage and administration.

Thorough reading and use of both this user manual and the Ameluz® USPI is required prior to treatment.

Our combination Ameluz®/BF-RhodoLED® for photodynamic therapy is only to be used by physicians or healthcare professionals.

For further questions about Ameluz®, BF-RhodoLED® or the combination therapy please contact your sales representative or Biofrontera (Ameluz-US@biofrontera.com). See contact information below:

<u>Sales representative:</u>	
Name:	_____
Tel.:	_____
E-mail:	_____

Biofrontera Inc.
201 Edgewater Drive
Wakefield, MA 01880
USA

Warranty and Disclaimers

Please see the terms and conditions of your contract for this information.

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1 Intended Use

BF-RhodoLED® is a red light emitting LED lamp which is used exclusively in combination with Ameluz® gel for lesion-directed and field-directed treatment of actinic keratoses (AKs) of mild-to-moderate severity on the face and scalp.

2 BF-RhodoLED® - General Description

BF-RhodoLED® is comprised of three main components, the lamp head, the easily adjustable scissor arm, and the mobile frame with castors for smooth transport. In addition, the lamp has a convenient touchscreen monitor, storage shelf, aids for positioning the lamp head and a variable speed patient fan that can be regulated throughout the treatment.

3 Warnings and Precautions



The BF-RhodoLED® has been developed for use in photodynamic therapy in combination with Ameluz®gel. Any other use or combination of use is prohibited.



During PDT side-effects such as application site erythema, pain, irritation, edema, pruritus, exfoliation, scab, induration and vesicles may occur. For further information please see Ameluz® USPI chapter 6.



The user manual must be read carefully prior to using the BF-RhodoLED®.



The BF-RhodoLED® may only be used by healthcare professionals who have received adequate training in its use.



To avoid eye irritation, glare, or injury, protective eye equipment must be used by patient, healthcare providers and any person present during the illumination period.



Neither the BF-RhodoLED® nor the power supply unit should be exposed to excessive mechanical stress or serviced by unauthorized personnel. Assembly and servicing may only be carried out by Biofrontera certified professionals.

Risk of trapping fingers! The mobility of the bracket arm may be obstructed by objects placed in or near slots!



Depending on positioning, the scissor arm slots below each connecting portion of the scissor arm and to the right of the support rail can cause fingers or objects to become trapped. When transporting or adjusting the lamp please ensure that fingers or other objects are NOT placed in or near the slots (see Figure 1).

Beware of Tipping!



If the castors are in locked position, the lamp will tip over if exposed to lateral force. Leaning against the device or using it for support is not permitted.

Do not place the lamp on uneven or unstable surfaces.

Do not place heavy objects on the storage shelf or use for sitting, leaning or pushing, as this can lead to the device tipping over.



In order to avoid the risk of electrical shock, the device may only be connected to a power supply with a grounded connection.



Neither the BF-RhodoLED® nor its touchscreen monitor may come into contact with water as this may lead to severe damage or electrical shock (exception: cleaning with a damp cloth).



The plexiglass plate may NOT be touched during or directly after treatment as, in the event of faulty operation, the maximum temperature can reach approx. 73 °C (163.4 °F).



The BF-RhodoLED® should be operated and housed indoors in areas with temperatures between 0°C and 40°C (32°F and 104°F), and relative humidity of 10 % to 90 %.



Medical electronic devices require special precautionary measures with regard to the electro-magnetic compatibility (EMC); to avoid elect-magnetic disturbances, please do not place the device close to other electrical devices.



There is a risk of tripping over the power cord or the lamp base. When transporting or when device is not in use, unplug and keep the power cord wound around the star knobs.



Ensure that the touchscreen monitor is always returned to the fixture intended for this purpose, located on the storage shelf. Storing the touchscreen monitor by hanging it can lead to damage to the spiral cord and the plug fitting.



The touchscreen monitor should not be exposed to strong external pressure or sharp objects.

Both the maintenance and the assembly of the BF-RhodoLED® and its components (including the opening of individual components) may only be carried out by professionals certified and trained by Biofrontera. In the event of servicing or assembly being carried out by any other party, Biofrontera assumes no responsibility or liability regarding the safety or use of the device.

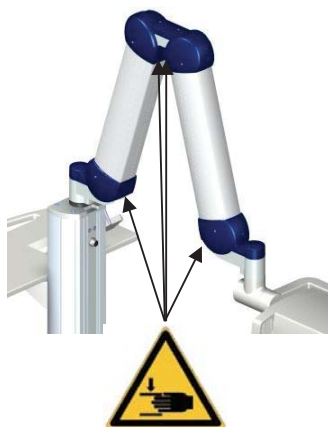


Figure 1: The scissor arm in parked position. Arrows indicate potential points where fingers can get trapped

4 BF-RhodoLED® Technical Description

4.1 Light Emitting Diodes (LEDs)

The light-field of the BF-RhodoLED® consists of a total of 128 LEDs and lenses (arranged in a rectangle), which emit a uniform, bundled, visible red light with a typical peak wavelength of approximately 635 nm. The half-band width of the lamp is 20 nm.

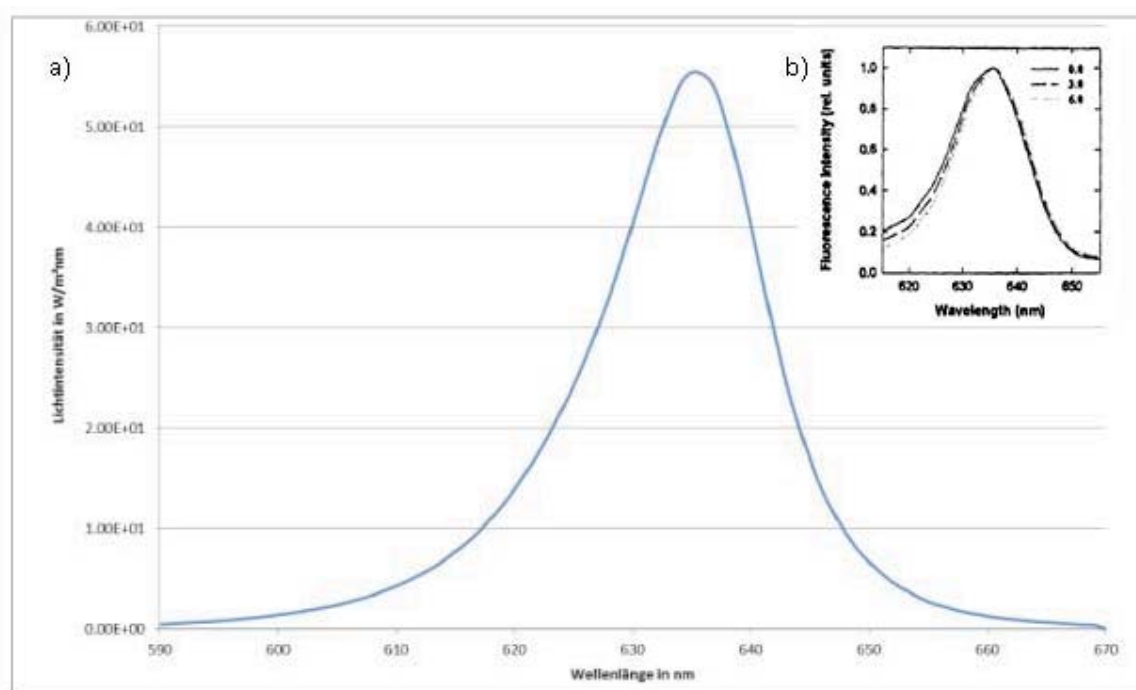


Figure 2: a) Typical light spectrum of the LEDs of the BF-RhodoLED®
 b) Absorption spectrum of PPIX in cells (Moan et al., 1996)

The BF-RhodoLED® LEDs are calibrated so that the skin being treated receives a light dosage of approximately 37 J/cm² under the following conditions:

- Radiation time of 10 minutes
- Treatment distance of 5-8 cm (Optimum 6 cm)

The illumination area of the LED lamp is 8 x 18 cm. As the intensity decreases towards the edge of this area, the effective treatment area is reduced to 6 x 16 cm.

4.2 Lamp Components

The BF-RhodoLED® LED lamp consists of the following components (figure 3):

- Lamp head with holding bracket
- Scissor arm
- Storage shelf with control unit (touchscreen monitor)
- Mobile frame and lamp base (includes support rail, castors and power supply)

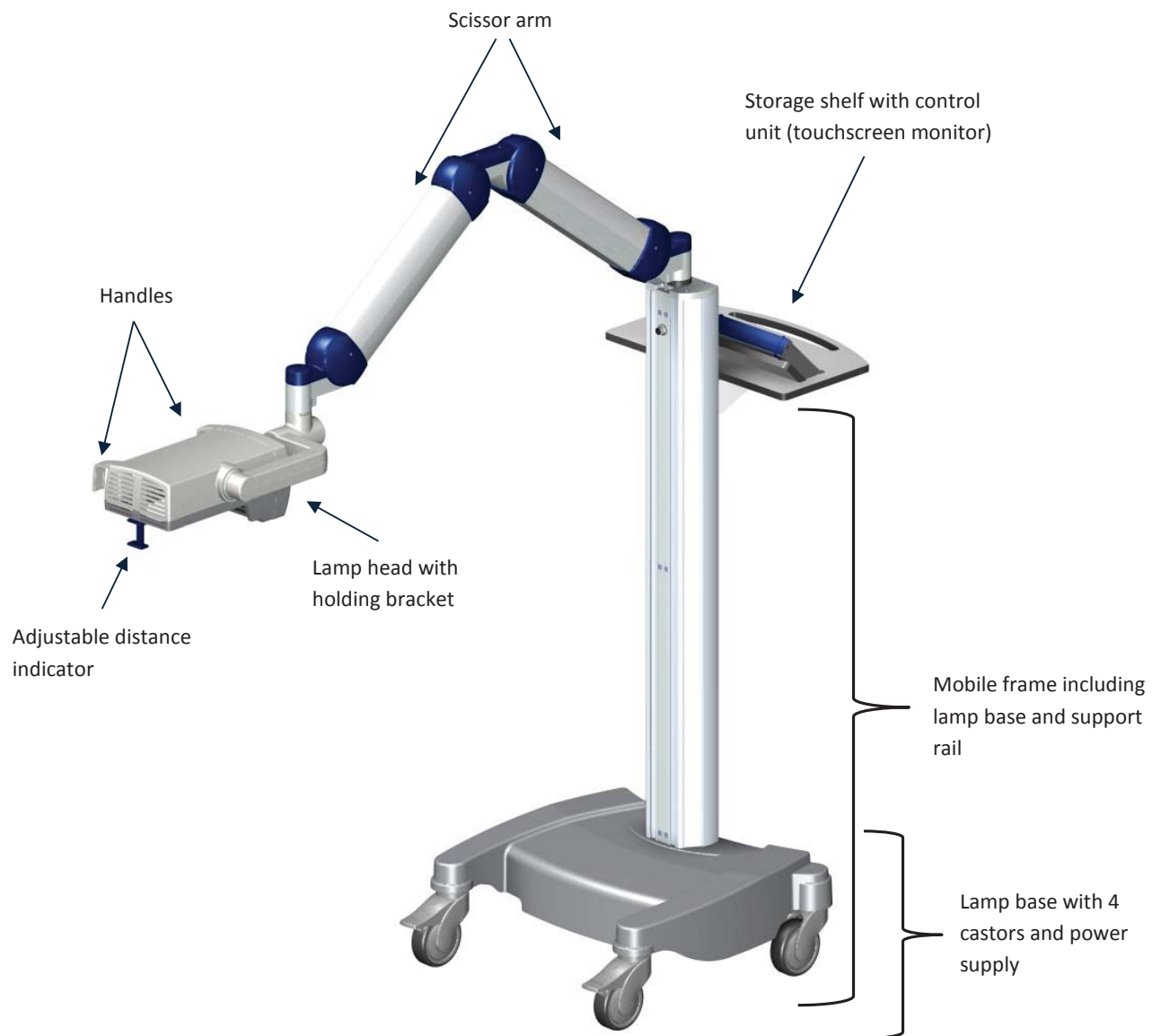


Figure 3: BF-RhodoLED® main components

The swivel range to the left and right of the vertical rail is $\pm 24^\circ$. The lamp head can be adjusted horizontally and vertically and tilted sideways. The scissor arm with internal gas springs allows seamless adjustment of the lamp head to any position.

5 Eye Protection

In order to avoid eye irritation, glare or injury, protective eye equipment must be used by patient, healthcare providers and any person present during the illumination period. Do not stare into the light source! The operator and other persons present must wear protective glasses with a visible light transmission (VLT) of approximately 10%. The patient must wear eye protection such as disposable eye protection pads or eye caps with an optical density for visible light of 6 or higher. Both options are effective and comfortable for use during treatment.

Note: Eyewear is not part of the medical device. Please carefully read any accompanying usage information before using any eye protection.

6 BF-RhodoLED® PDT Summarized Step-by-Step Instructions

These instructions should be used in conjunction with detailed operating instructions below (chapter 7). The section titles and numbers listed next to the instruction refer to the detailed instructions and/or descriptions that correspond with each step.

- STEP 1) Plug in lamp.
- STEP 2) Turn on the lamp and wait for home screen to appear (see chapter 7.1).
- STEP 3) Position patient comfortably and prepare skin area to be treated following the USPI of Ameluz®.
- STEP 4) Place protective eyewear on patient (see chapter 5).
- STEP 5) Position the lamp and adjust the lamp head over the skin area to be treated (distance 5-8 cm) (see chapter 7.3.1).
- STEP 6) Put on protective eyewear and make sure anyone remaining in the treatment room also wears protective eyewear.
- STEP 7) Start treatment by pressing “Treatment” on the home screen, press “Start” on the treatment screen, and press “Start” once again in the profile screen. The illumination period of 10 minutes begins (see chapter 7.3.2).
Remind the patient to remain still throughout the illumination period.
If sound tone during treatment is activated, explain the beep sequence to the patient.
If the patient needs a break, press “Break” on the profile standard screen. To resume treatment, press “Start” on the profile standard screen (see chapter 7.3.2).
To abort the illumination, press “Stop” on the profile standard screen.
Adjust fan speed as needed by patient by pressing plus or minus 1% or 10% on the profile standard screen.
Stay with the patient at all times during the illumination period.
- STEP 8) At the end of the illumination period, remove patient’s protective eyewear and follow further instructions in the Ameluz® USPI.

7 Detailed Operating Instructions

Note: Before turning on the lamp, the power cord must be plugged in. After connecting, the lamp can be turned on and used following the instructions below.



In order to avoid eye irritation, glare or injury, protective eye equipment must be used by patient, healthcare providers and any person present during the illumination period.

7.1 Turning the Lamp On or Off

The on-off switch is located on the left side of the touchscreen monitor, close to its spiral cord. With the lamp plugged in, press the button to start the device.

Important: This push button can also be used to turn the lamp off. Switching off the lamp can also be done by pressing the switch off  button on the touchscreen (see chapter 7.2.2 "Home Screen").



Figure 4: Touchscreen monitor

7.2 Touchscreen Monitor and Menu

When using the touchscreen, please firmly press the center of the buttons shown on the screen to ensure it is read correctly by the software. Do not press too quickly, the input may not be read by the software. The touchscreen can be used while wearing commercially available examination gloves.

7.2.1 Start Screen

The Biofrontera corporate logo and software version are displayed during the LED lamp operating system start-up (figure 5). The operating system takes approximately 30 seconds to load.



Figure 5: Start screen

7.2.2 Home Screen

The home screen appears after the operating system has loaded. From the home screen you can select "Treatment", "Settings" or "Service" (Figure 6). In the "Treatment" menu only one treatment profile "profile standard" is available. The illumination time and light intensity of this program are fixed (see 7.3.2 for further information). The "Settings" menu allows adjustment of language, time, date, audio signals and power saving settings (see 7.4 for further information). The "Service" menu may only be accessed by Biofrontera service technicians. You can turn the LED lamp off by pressing the  button.

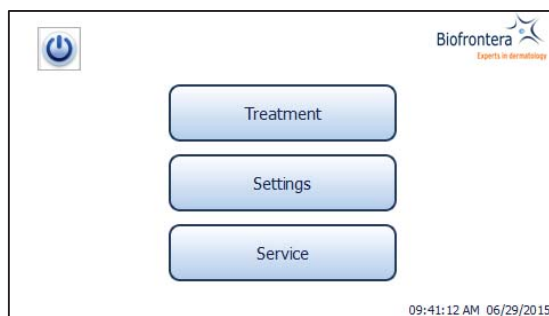


Figure 6: Home screen

7.3 Conducting a Treatment

Prior to starting a treatment, make sure the lamp is set-up in accordance with the operating instructions described in the following sections.

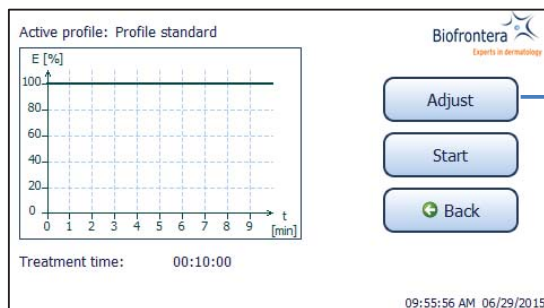
7.3.1 Positioning the Lamp Head

Position the lamp head over the skin area to be treated at a distance of 5-8 cm. Use the adjustable distance indicator and graduated scale bar to help measure and aid in achieving the correct distance (figure 7).



Figure 7: Positioning of the lamp head to the treated skin area

To further aid positioning, use the adjustment light. On the touchscreen, press the following buttons in sequence (starting in the home screen): “Treatment”, “Adjust” and “Start Adjustment” (figure 8). The adjustment light shows what the field of illumination will be during treatment but at a lower intensity. When finished, press “Stop adjustment” and then “Back” to return to the treatment menu (figure 9).



Takes you to adjustment screen shown below. Used to aid in lamp head positioning prior to treatment.

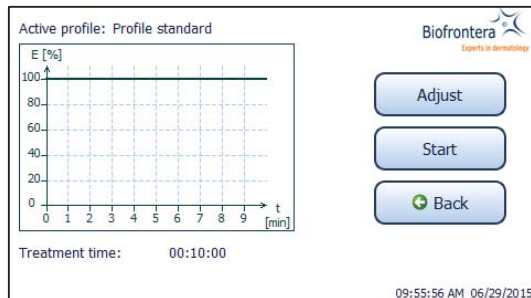
Figure 8: Treatment menu



Figure 9: Start and Stop adjustment

7.3.2 Treatment Menu

The standard illumination profile is depicted in a graph in the treatment menu. The x- and y-axis specify the treatment duration and light intensity respectively (Figure 13).



- Takes you to light head positioning
- Takes you to profile standard
- Takes you to home

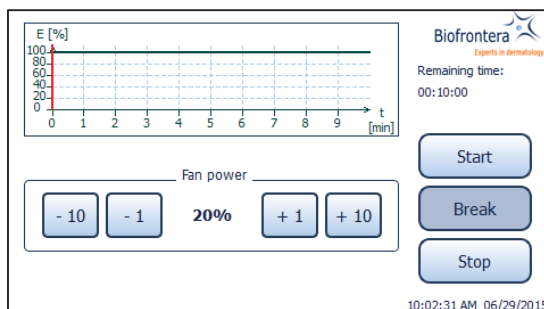
Figure 10: Treatment menu

In the treatment menu (figure 10), press the "Start" button to access the profile standard screen.

7.3.3 Profile Standard Menu

In the profile screen menu, press "Start" to begin treatment (figure 11). You can interrupt the treatment at any time by pressing the "Break" button. Press the "Start" button to resume the treatment. Abort the current treatment by pressing the "Stop" button.

If you press "Stop" prior to the end of the total treatment time, 10 minutes, the clock will reset and any interim treatment time will not be saved.



- Press to begin treatment
- Press to pause treatment
- Press to abort treatment

Figure 11: Profile standard

After pressing "Stop" or upon completion of the full 10 minute treatment the software will automatically return you to the treatment menu.

The remaining treatment time is displayed to the right of the graph and the red vertical line within the graph indicates the time that has elapsed.

During treatment the patient will hear audio signals, 1 beep indicating 25 %, 2 beeps indicating 50 % and 3 beeps indicating 75 % of the PDT is completed, and upon treatment completion, 4 beeps will be heard.

You can control the speed of the patient fan both before and during treatment with the plus and minus buttons, in increments of 1 % or 10 %. The patient fan continues to run when the treatment is paused ("Break"). The fan can be stopped by pressing "Stop" but be aware the treatment will also be aborted and any elapsed treatment time will not be saved.

7.4 Settings Menu

The settings menu is invoked (figure 15) by pressing the "Settings" button in the home screen view (see figure 9).



Figure 12: Settings menu

You can configure the following parameters in this menu:

- Language
- Time
- Date
- Signals
- Energy service (Power management)

Switch back to the home screen menu via the "Back" button.

7.4.1 Language Settings

Select a language by tapping on the desired language. Use the arrow keys to scroll through the list. Confirm the selected language with the "OK" button (figure 13). Switch back to the settings menu without saving changes by pressing the "Back" button instead of "OK".

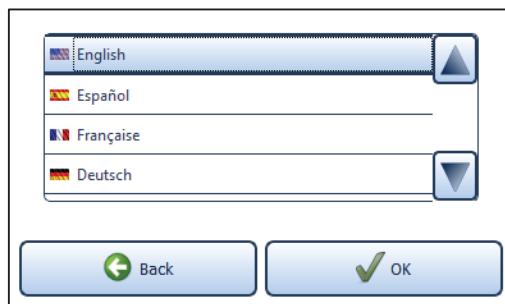


Figure 13: Language setting

7.4.2 Time Settings

Set the time via the plus and minus buttons and confirm by pressing "OK" in the menu shown in figure 14. Confirm your selection by pressing "OK". Pressing "Back" or "OK" will return you to the settings menu.

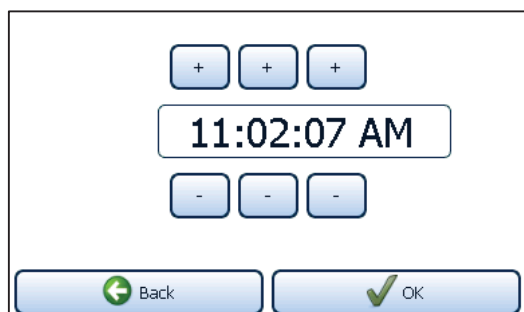


Figure 14: Time settings

7.4.3 Date Setting

Select the date by clicking on it and confirm by pressing the "OK" button (figure 15). Pressing "Back" or "OK" will return you to the settings menu (figure 12).



Figure 15: Date setting

7.4.4 Sound Settings

Activate and deactivate the audio signals for typing, warnings and sounds during the treatment. To do this, select the desired fields, a check mark means the sound is on and confirm with the "OK" button (figure 16). If "Turn off sound" is activated, all signal tones are switched off. Upon completing set-up, close the menu via the "Back" button. You will be returned to the settings menu.

Important Note: Warning sounds will be emitted if an error occurs during operation of the lamp.

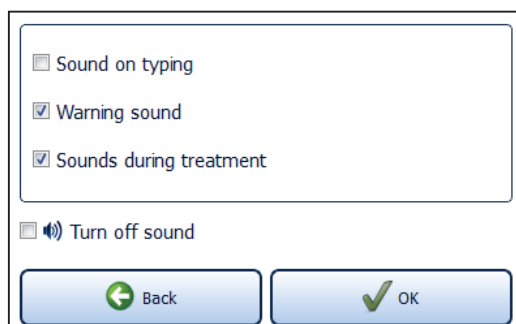


Figure 16: Sound setting

7.4.5 Energy Service (Power Management)

Providing the standby function is not manually deactivated via the check box "Never turn off lamp automatically" located near the bottom of the screen, the lamp will turn off after 10 minutes of non-use (figure 17). You can change this time span in the menu "Energy service" via the plus and minus buttons. The settings are confirmed with the "OK" button and rejected with the "Back" button. In both cases you will return to the settings menu.

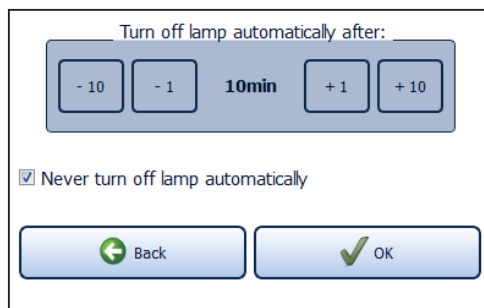


Figure 17: Energy management

If the configured time expires, a request appears for 10 seconds asking if you wish to prevent shut down. The LED lamp turns off automatically afterwards.

7.5 Service Menu

Authorization is required to access the service menu. Only authorized Biofrontera personnel can access the service menu.

8 Error Messages

The BF-RhodoLED® has an integrated monitoring function. In the event of a malfunction, an error message will appear in the message display. Possible error messages are set out in the table below.

Error message	Possible causes	Measures
Lamp overheated!	- The temperature of the surrounding environment is too high. - The ventilators or ventilator slots are blocked. - The air inlets or outlets are adversely affected.	Wait until the standard temperature has been reached. Check the ventilator and test the air inlets and outlets. Remove any visible foreign objects which may be present. In case of continuing impairment of cooling please contact your local sales representative or Biofrontera.
Service required!	Service is required within 4 months or after 2000 operating hours	A service is required soon. Please contact your local sales representative or Biofrontera.
Service required! Treatment no longer possible!	The service interval has expired and further treatments are not possible.	Certain service is mandatory. Please contact your local sales representative or Biofrontera.
Lamp error! Please inform your supplier.	Some of the LEDs have failed.	Further treatments may be carried out. However, please contact your local sales representative or Biofrontera immediately.
Lamp error! Treatment no longer possible.	Too many LEDs have failed. Sufficient illumination can no longer be guaranteed.	A repair of the lamp head is mandatory. Please contact your local sales representative or Biofrontera immediately.
Communication error!	- Cable break in the touchscreen monitor spiral cord. - Poor contact between the touchscreen monitor connection plug and the conduit box.	Confirm the communication error. Treatments can be continued in the treatment menu by pressing the "Start" button. Please contact your local sales representative or Biofrontera.
Lamp not calibrated!	- The lamp is not calibrated. - Improper calibration.	The lamp has to be calibrated. Please contact your local sales representative or Biofrontera immediately.
Fehler-Nr.: 0084 Please	A temperature sensor has	The lamp head has to be

inform your supplier.	failed.	repaired. Please contact your local sales representative or Biofrontera.
Firmware of light head is faulty or missing! Please inform your supplier.	An Update of the firmware has to be performed.	An update of the firmware has to be performed. Please contact your local sales representative or Biofrontera.
Backup battery empty	Backup battery of the touchscreen monitor is nearly drained. The lamp can no longer reliably store data.	The backup battery has to be promptly exchanged. Please contact your local sales representative or Biofrontera.

If your LED lamp no longer functions properly for some unknown reason, proceed as follows:

- Unplug the power supply for half a minute and then plug back into the outlet (This action prompts a software reboot).
- Turn the lamp back on using the touchscreen monitor and verify functionality.

Should the problem persist, please contact your sales representative or Biofrontera. The lamp may not be used until the problem has been rectified.

For all other malfunctions and difficulties with operation please contact your sales representative or Biofrontera. You will find the contact details on page 2.

9 Servicing

Servicing may only be performed by Biofrontera authorized personnel or duly authorized licenced partners.

Maintenance of the light intensity (calibration) is required after every 12,000 hours of operation or every 2 years, whichever comes sooner. The message "Service required" will appear on the touchscreen monitor 20 months after initial installation or last calibration or after 10,000 operating hours. When this message appears, a maintenance appointment must be scheduled through your sales representative or the device will ultimately not allow further treatments.

The gas springs in the scissor arm of the lamp must also be serviced and, if required, readjusted annually.

Contact your sale's representative or Biofrontera to schedule all service appointments.

10 Maintenance and Cleaning

The device may under no circumstances be cleaned with aggressive cleaning agents or solvents (e.g. acetone), as these promote wear and tear of the surface (paint coating), safety signs and graduated scale bar as well as the logo. Please avoid allowing any penetration of liquids into the lamp, BF-RhodoLED® is not waterproof and the electronics inside may be damaged.

Always unplug the lamp prior to cleaning and please observe the following cleaning practices:

Daily: Wipe the plexiglass screen located on the bottom of the lamp head with a damp soft cloth (e. g. a microfibre cloth).

Weekly: Wipe the entire lamp with a soft, dry or damp cloth. Do not use a very wet or dripping cleaning cloth. The unit is not waterproof and damage could occur.

Please observe the following checks:

Monthly: Check lamp for obvious visible damage such as damaged cables, worn off labeling, cracks on the lamp housing, etc.

11 Disposal Instructions

Follow all local and governmental disposal laws and regulations when disposing of the BF-RhodoLED®.

12 Technical Data

12.1 Electrical connectors

Power supply unit:

- Primary wide-range input 120-240 VAC
- Secondary safety extra-low voltage output 48 VDC
- Secondary standby voltage output 5 VDC

Mother board for voltage management and control:

- Supply voltage input 48 VDC
- Standby voltage input 5 VDC plus Standby contact
- RS485 interface
- Output supply voltage HMI board 24 VDC
- 4 x ports LED board 8-pin (2 x LED circuits, temperature (3-pin))
- 4 x connector ventilator (2-pin)

LED board:

- 2 x ports mother board 8-pin (2 x LED circuits, temperature (3-pin))

Human Machine Interface (HMI) for operation:

- Supply voltage input 24 VDC
- RS485 interface

12.2 Specification

Type	BF-RhodoLED® Medical device class III; Device of protection class 1
------	--

Software Version No.	1.0_US_CAN
Service life of the lamp	Approx. 4 years of continuous operation
Shelf life	1.5 years
Number of LEDs	128
Typical peak wavelength	Approx. 635 nm
Light dose (6 cm distance, 10 min)	Approx. 37 J/ cm ²
Illuminated area	An area of 8x18 cm is illuminated. The effective treatment area is 6x16 cm.
Transport and storage conditions	Temperature: -30°C to +60°C (-22°F to +140°F) Atmospheric pressure: 500 hPa - 1060 hPa Relative humidity: 10% - 90%, non-condensing
Operating conditions	Temperature: 0°C to +40°C (32°F to +104°F) Atmospheric pressure: 500 hPa - 1060 hPa Operational altitude: ≤ 2000 m above NN Relative humidity: 10% - 90%, non-condensing This PDT lamp is suitable for <u>continuous operation</u> !
Operating voltage	120-240 VAC, 50/60 Hz
Output voltage	48 VDC
Power consumption	In calibrated normal operation: approx. 140 VA In standby mode: approx. 85 VA
Over-voltage category	II
Degree of contamination	2
Material group (CTI)	IIIb
Protection class	IP20
Total lamp weight	Approx. 48 kg

For further information please directly contact Biofrontera.

13 Labeling and Symbols

13.1 Labelling on the Lamp

The product sticker is located on the reverse side of the lamp base (see figure 18). It contains manufacturer and product specifications (classification, serial and order number and the power supply used) as well as IP (Ingress) protection. In addition a unique device identifier label is placed next to the product sticker.

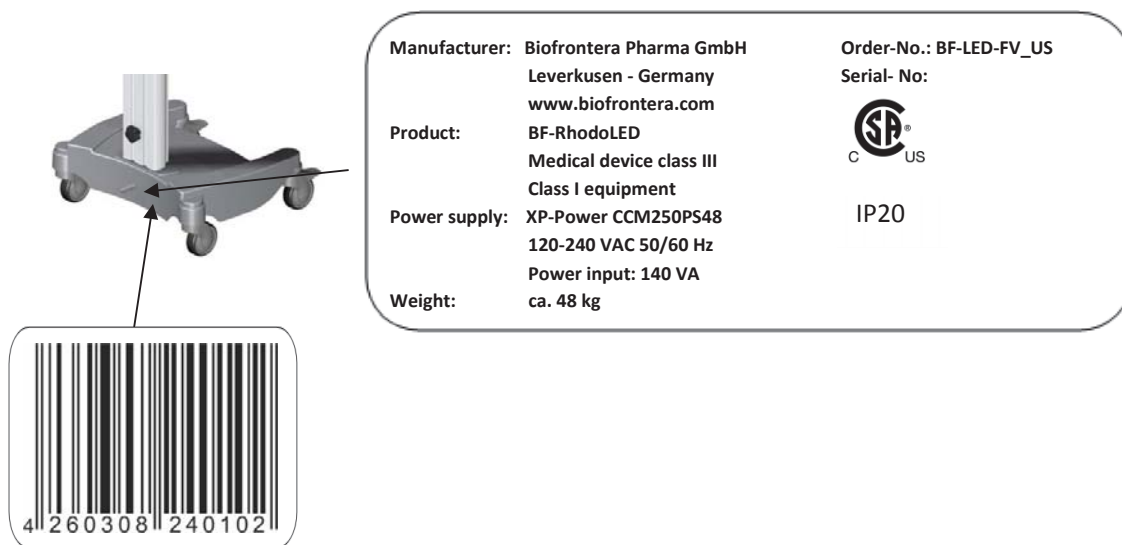


Figure 18: Product and UDI label

Labels with safety instructions, special disposal instructions and further instructions are represented in the following figures 19 to 24.

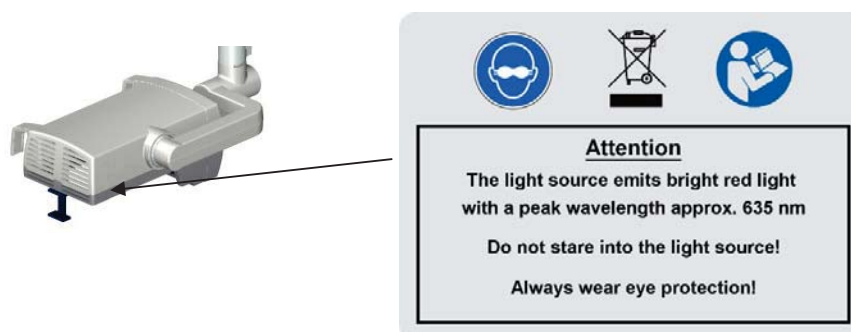


Figure 19: Instructions and notes on the lamp head

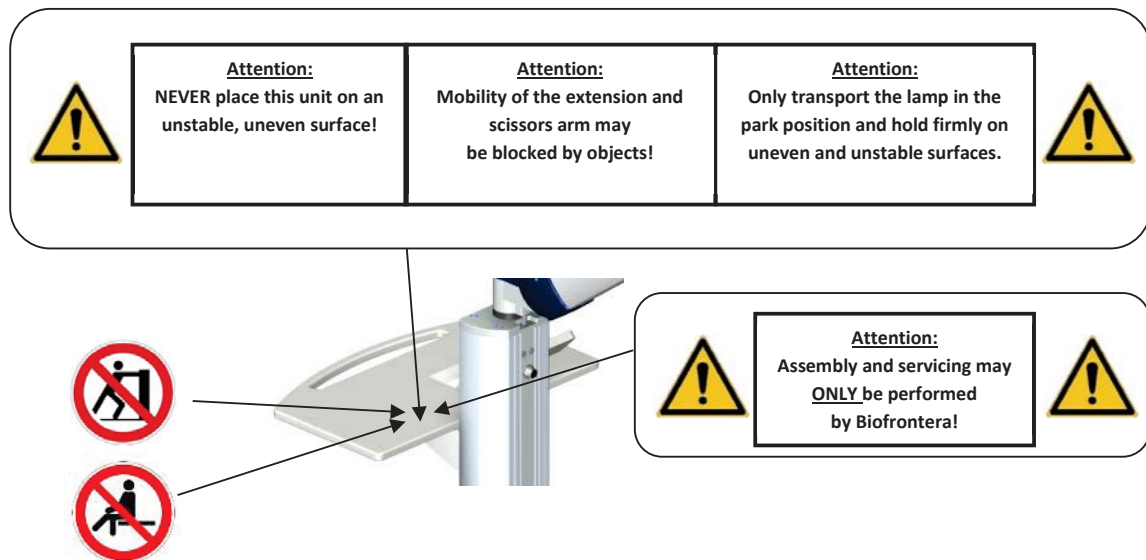


Figure 20: Instructions on the storage shelf



Figure 21: Instructions on the scissors arm

Instructions for existing ground connector connections (see figure 22) are located:

- Next to the grounding screws, which are located within and next to the power supply cover box beneath the mobile castor, respectively
- On the power supply cover box (see figure 23)



Figure 22: Instructions for ground connector connection



Figure 23: BF-RhodoLED®

Instructions on the existing potential compensator conductor is located on the carrier bar beneath the potential compensator conductor (see figure 24).



Figure 24: Potential compensator conductor

All depicted symbols are summarized in a table in section 13.2 "Explanation of symbols".

13.2 Description of Symbols

Symbol	Description
	Eye protection is required.
IP20	IP (Ingress Protection): Protection class of the housing against contact, foreign bodies and water 2 = against ingress of solid foreign bodies $\geq 12,5$ mm $\varnothing$ and larger 0 = <u>Not</u> protected against water
	Technical and electric devices must not be disposed of with household waste. Please pay attention to the applicable disposal instructions found in the user manual.
	Symbol for existing ground connector connections
	Follow the instructions for use!
	<u>General warning signs:</u> • Assembly and servicing may <u>ONLY</u> be performed by Biofrontera! • Only transport lamp in the park position! • The mobility of the extension and scissors arm may be obstructed by objects! • Caution: heavy, do NOT lift alone. • NEVER place this unit on an unstable, uneven surface!
	Warning sign - risk of trapping fingers!
	Symbol for existing potential compensation conductor
	Please do not stand on or push. There is a risk that the device may fall over through of the force applied.
	Please do not sit on the equipment. There is a risk that the device may fall over through the force applied.

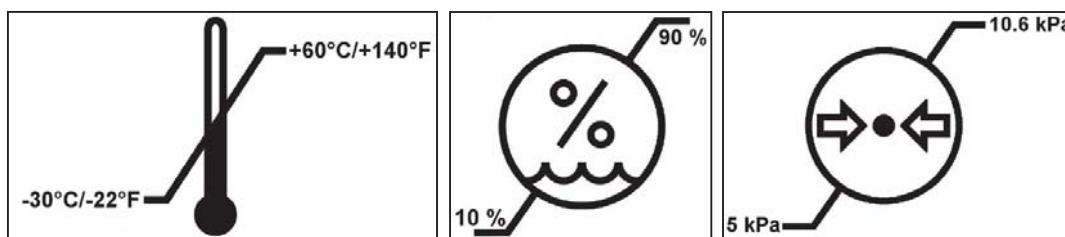
13.3 Labelling on the Packaging

- Package 1 and 2: Attention: Protect from moisture and keep dry!

Vor Nässe schützen
Keep dry



- Package 1 and 2: Attention: Please transport and store at -30°C/ -22°F to +60°C/ 140°F, a relative humidity of 10% to 90% and at an atmospheric pressure of 500 hPa (5 kPa) - 1060 hPa (10,6 kPa).



- Package 1 and 2: Attention: Do not throw the package, damage possible!



- Package 2:  Attention: heavy, do NOT lift alone.
- Labelling of the individual packages with package 1 and package 2
- Package 1:  Attention: Stack to a maximum height of two packages!



- Package 2:  Attention: Do not stack!



- Package 1:  Attention: The extension and scissors arm of the unit consisting of lamp head, lamp holder and extension and scissors arm is packed in a taut position. When removing from its packing case, please ensure that the extension and scissors arm is in a taut position under reciprocal pressure in order to release easily.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KENDALL A MARCUS
05/10/2016