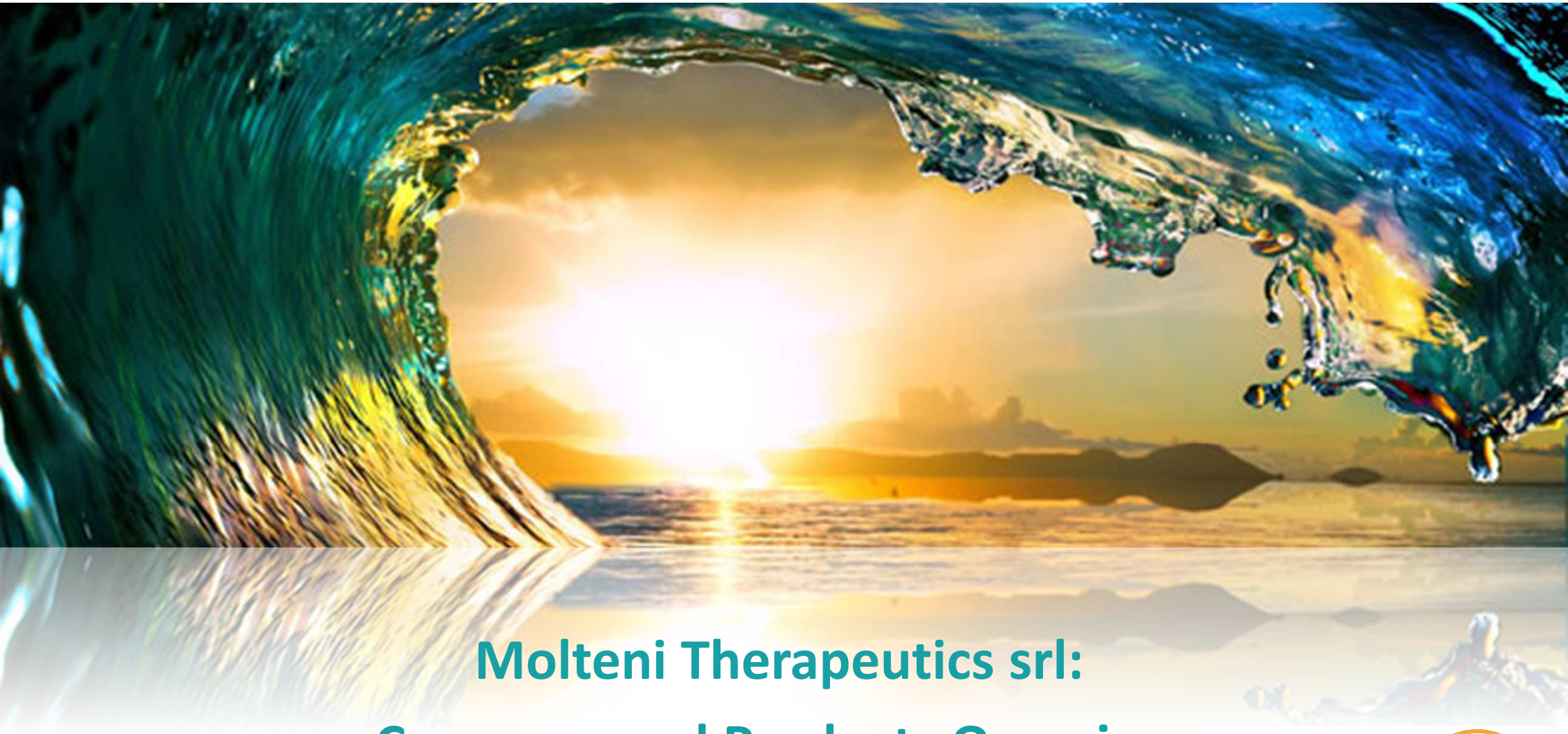

Molteni Therapeutics srl:

Company and Products Overview

MOLTENI
THERAPEUTICS

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WHO WE ARE

Founded in November 2006 as a *spin-off* of Molteni Farmaceutici, an Italian company with more than a century of pharmaceutical experience.

Molteni Therapeutics is a product driven company dedicated to the development of innovative Medical Devices, principally based on the Photodynamic Therapy technology, to meet *unmet medical needs*.

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OUR VISION

Molteni Therapeutics focuses its activities on design and development of New Medical Devices and new Photo Dynamic Therapy (PDT) based therapeutic approaches to the management of skin lesions and ulcers, both uninfected and infected .

« ***Molteni Therapeutics believes that PDT will become the best and widespread therapeutic approach triggering wound healing. PDT is effective and safe. In exerting its activity on infecting microorganisms, PDT does not induce drugs resistance and overcomes this threat. PDT is easy to use.*** »

Dr. Giuseppe Seghi Recli - CEO Molteni Therapeutics

OUR MISSION

Molteni Therapeutics is dedicated to the development of innovative Medical Devices based on the **P**hoto **D**ynamic **T**herapy **(PDT)** in the field of **WOUND CARE** and the management of **skin lesions and ulcers.**

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OUR CERTIFICATIONS

The Quality Management System (QMS) of Molteni Therapeutics is certified by TÜV Italia for:

"Design and development, management of production and marketing of non active medical devices for treatments of skin lesion and ulcers (solutions for photodynamic treatments (PDT)). Management of design and production, marketing of active medical devices for photodynamic treatments. Management of production and marketing of applicator for subcutaneous implants "

according to the following International Standards:

- **UNI EN ISO 9001:2015** (Quality management systems - Requirements)
- **UNI EN ISO 13485:2016** (Standards for Quality Management System on Medical Devices)

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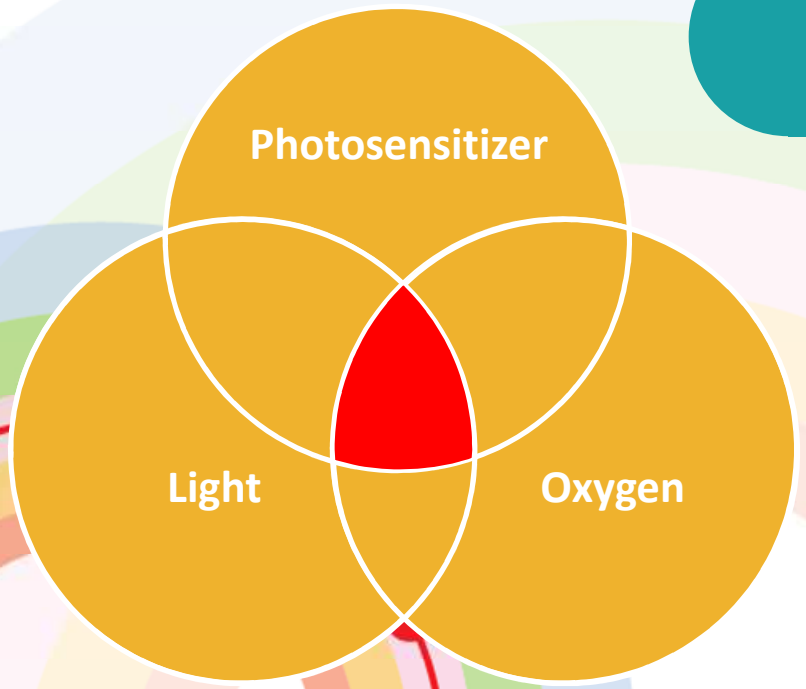
MODE OF ACTION



PDT combines the effect of three intrinsically non-toxic elements

Molteni Therapeutics was a pioneer in exploiting the PDT technology and developing topically administered products for the treatment of uninfected and infected skin lesions and ulcers .

The photosensitizers activity depends on the production of singlet oxygen ($^1O_2$) or other Reactive Oxygen Species (ROS) which rapidly restore the micro-environment of the lesion, promoting a wound healing effect.

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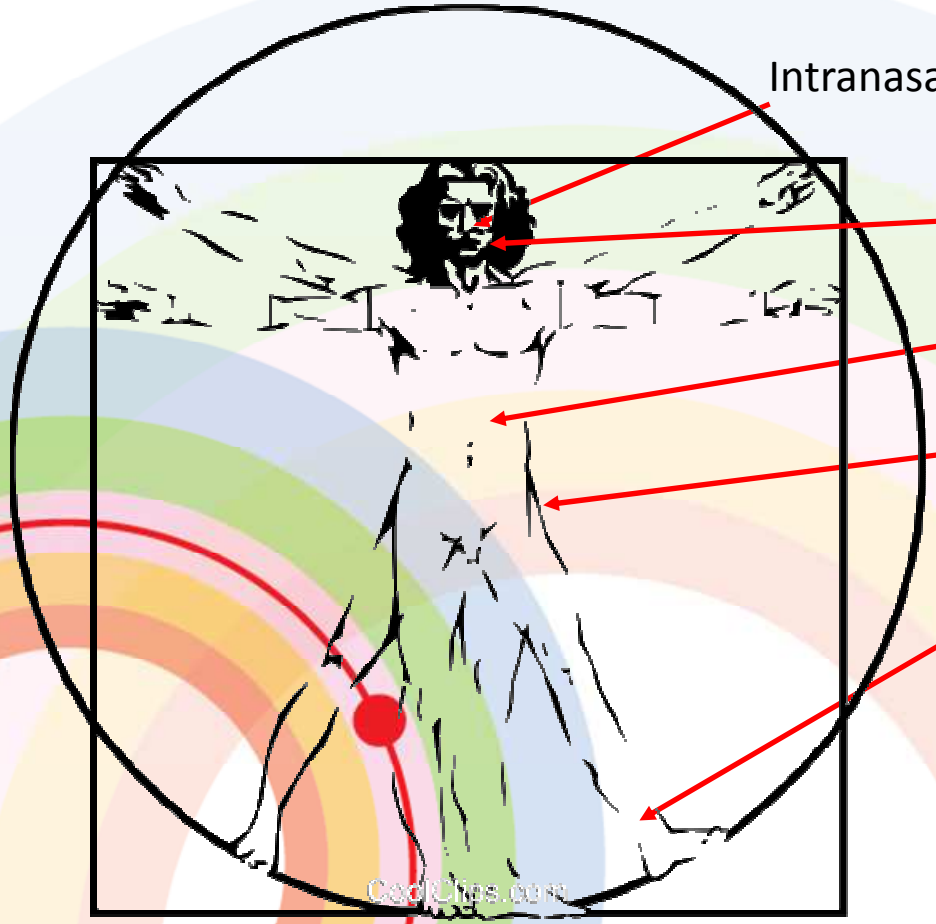
ADVANTAGES

- Healing promoting activity and an immediate reduction of the bacterial load
- Broad spectrum of antimicrobial activity, including wild type and resistant strains
- No induction of resistance *in vitro* by multiple PDT treatments

- Excellent safety and tolerability profile, safe for host tissues
- No interference with normal tissues or bacterial flora outside the lesion
- Negligible systemic exposure (photosensitizer is topically applied)

- Proven trigger and improvement of wound healing of infected lesions and ulcers but also in non infected lesions
- Co-adjuvant of systemic antibiotic regimens (if clinically required)

THERAPEUTIC AREAS



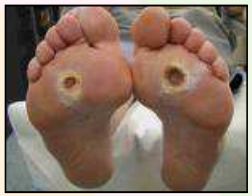
Intranasal Bacterial Infectious disease

Periodontal disease

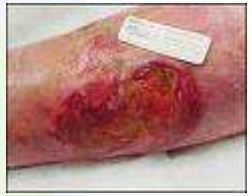
Dermatological Infectious disease and cancerous or precancerous lesions

Prosthesis infections

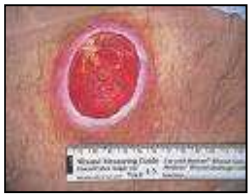
Chronic ulcers treatment



Diabetic foot ulcers (DFU)



Chronic leg Ulcers (vascular)



Post trauma, surgical, pressure ulcers, burns

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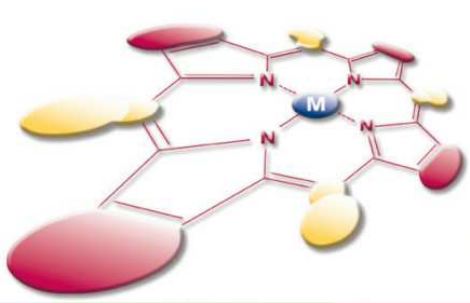
APDT EARLY DEVELOPMENT Q-SAR STUDIES



Journal of Porphyrins & Phthalocyanines

Phthalocyanines as photodynamic agents for the inactivation of microbial pathogens

Donata Dei*[a◇], Giacomo Chiti[a], Maria P. De Filippis[a], Lia Fantetti[a], Francesco Giuliani[b], Francesca Giuntini[a], Marina Soncin[a], Giulio Jori[c◇] and Gabrio Roncucci[a]

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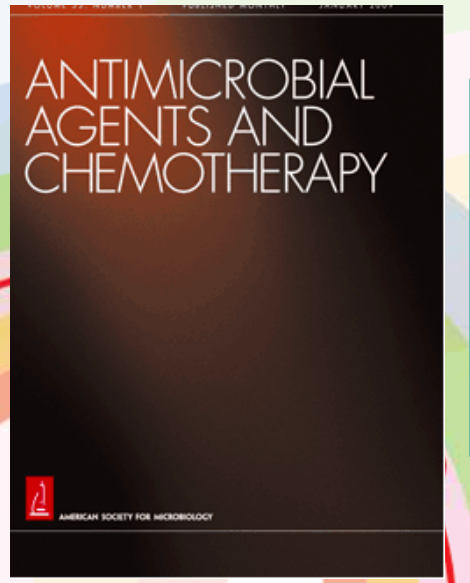
Received 22 February 2006
Accepted 1 May 2006

Ver. Dec 2018

NO RESISTANCE INDUCED

No induction of resistance experimentally demonstrated by multiple APDT treatments



In Vitro Resistance Selection Studies of RLP068/Cl, a New Zn(II) Phthalocyanine Suitable for Antimicrobial Photodynamic Therapy▽

Francesco Giuliani,* Manuele Martinelli, Annalisa Cocchi, Debora Arbia, Lia Fantetti, and Gabrio Roncucci

Molteni Therapeutics srl, Via Fiorentina 1, 53100 Siena, Italy

Received 4 May 2009/Returned for modification 5 June 2009/Accepted 1 December 2009

Ver. Dec 2018

APDT- Scientific Community endorsement

THE LANCET
Infectious Diseases

Published Online
November 21, 2016

Photoantimicrobials—are we afraid of the light?

Mark Wainwright, Tim Maisch, Santi Nonell, Kristjan Plaetzer, Adelaide Almeida, George P Tegos, Michael R Hamblin

Although conventional antimicrobial drugs have been viewed as miraculous cure-alls for the past 80 years, increasing antimicrobial drug resistance requires a major and rapid intervention. However, the development of novel but still conventional systemic antimicrobial agents, having only a single mode or site of action, will not alleviate the situation because it is probably only a matter of time until any such agents will also become ineffective. To continue to produce new agents based on this notion is unacceptable, and there is an increasing need for alternative approaches to the problem. By contrast, light-activated molecules called photoantimicrobials act locally via the in-situ production of highly reactive oxygen species, which simultaneously attack various biomolecular sites in the pathogenic target and therefore offer both multiple and variable sites of action. This non-specificity at the target circumvents conventional mechanisms of resistance and inhibits the development of resistance to the agents themselves. Photoantimicrobial therapy is safe and easy to implement and, unlike conventional agents, the activity spectrum of photoantimicrobials covers bacteria, fungi, viruses, and protozoa. However, clinical trials of these new, truly broad-spectrum, and minimally toxic agents have been few, and the funding for research and development is almost non-existent. Photoantimicrobials constitute one of the few ways forward through the morass of drug-resistant infectious disease and should be fully explored. In this Personal View, we raise awareness of the novel photoantimicrobial technologies that offer a viable alternative to conventional drugs in many relevant application fields, and could thus slow the pace of resistance development.

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APDT- Scientific Community endorsement

THE LANCET
Infectious Diseases

Published Online
November 21, 2016

	Chemical class	Wavelength	Spectrum of activity	Pathogen or type of infection treated	Clinical trial registration (used to treat, last updated)
Methylene blue	Phenothiazinium	Red 660 nm	Broad	MRSA surgical site, chronic sinusitis, periodontitis, halitosis,[60] oral candidiasis, oral mucositis (phase 3), severe sepsis and septic shock (phase 3), and onychomycosis[61]	NCT02555501 (mucositis, 2015), NCT01854619 (sinusitis, 2013 ongoing), NCT02007993 (halitosis, 2014 ongoing), NCT02407379 and NCT01535690 (periodontitis, 2015 and 2012), and NCT01981460 (skin pathogens and blood infections, 2013)
Toluidine blue O	Phenothiazinium	Red 660 nm	Broad	Wounds, burns, diabetic ulcers,[62] periodontitis[63] (phase 2), and carious dentin lesion (phase 1)	NCT02479958 (carious dentin, 2015) and NCT01330082 (periodontitis, 2011 ongoing)
PPA904	Phenothiazinium	Red 660 nm	Broad	MRSA, *Pseudomonas aeruginosa*, chronically non-healing streptococcal wounds,[64,65] and periodontitis	NCT00825760 (leg ulcers, 2013)
RLP068	Phthalocyanine	Far red 670–780 nm	Broad	MRSA skin abrasion, and diabetic foot ulcers	EudraCT Number: 2010-019598-13
ALA-PPIX	Porphyrin	Red 630 nm	Narrow	*Propionibacterium acne* and acne vulgaris,[66] chronic skin ulcers, and *Pseudomonas aeruginosa*	NCT00706433 and NCT01689935 (acne, 2011 and 2013)
Indocyanine green	Indocyanine	Near infrared 810 nm	Narrow	*Propionibacterium acne*, acne vulgaris,[67] and periodontitis	NCT02043340 (periodontitis, 2014)
Curcumin	Curcuminoid	Blue 420 nm	Narrow	Oral disinfection (phase 1), and oral mucositis (phase 1 or 2)	NCT02152475 (oral disinfection, 2014) and NCT02337192 (oral decontamination agent and mucositis infections, 2015 ongoing)
Riboflavin	Flavin	Blue 360 nm	N/A	Infectious keratitis[68]	NCT01739673 (keratitis, 2015)
PEI-ce6	Chlorin	Red 660 nm	Broad	Endodontic infection[69]	IRB approved trial in São Paulo, Brazil

All clinical trial phases are completed unless otherwise stated as ongoing. MRSA=meticillin-resistant *Staphylococcus aureus*. PPA904=tetrabutyl derviative of methylene blue. RLP068=tetracationic Zn(II) phthalocyanine chloride. ALA-PPIX=5-aminolevulinic acid-induced protoporphyrin IX. N/A=not applicable. PEI-ce6=polyethyleneimine chlorin(e6) conjugate. IRB=institutional review board.

Table: **Photoantimicrobials in clinical trials**

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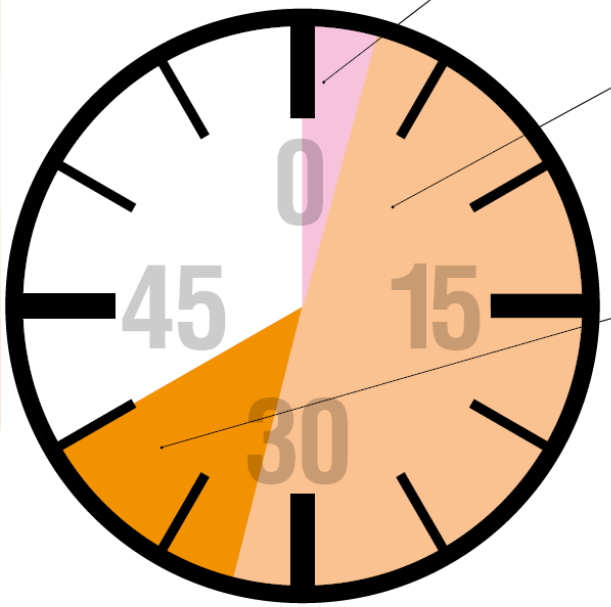
EASY TO USE THERAPEUTIC APPROACH

40 min session to be performed by physicians or trained nurses when applied to uninfected and infected skin wounds and ulcers



Step 1: Preparation of wound as usual

Step 2: Application of Vulnofast® / Elkofast®. 2 min

Step 3: Sufficient time should be allowed to allow the photosensitizer to saturate all relavant cell and microorganisms structures. Currently, estimated in 30 min

Step 4: Illumination. 8 min

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INTENDED USE

VULNOFAST® and ELKOFAST® are **topically** administered Medical Devices, recommended as **adjuvant** for the local treatment of **skin lesions and ulcers as part of** Photodynamic Therapy.

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PRODUCTS

VULNOFAST® gel 0.3%

Classification: class IIb Medical Device (CE_{0373} mark certification valid until 2023)

Sterile product

Visual aspect: gel formulation with viscosity of 50000-190000 cP

Product presentation: amber glass vials, sterile, pyrogen free closed with a Flurotec Plus coated chlorobutyl stoppers and aluminium tear off seal.

Each marketable unit contains 4 single use vials (2.5 g of gel formulation)

Product shelf life: 24 months for storage between 4°C and 25°C

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PRODUCTS

VULNOFAST® plus

Classification: class IIb Medical Device (CE_{0373} mark certification valid until Feb 2023).

Sterile product

Visual aspect: liquid formulation with viscosity of 25-65 cP

Product presentation: strip of sterile, gamma irradiated 2 ml LDPE UDV (5 UDV/strip). Each strip is enclosed in aluminium

Single dose container of 2.0 g of liquid formulation

Product shelf life: 36 months for storage under 25°C

Manufacturing

- batch size: 100 kg, 6500 marketable units, 32500 single dose containers
- batch size: 300 kg, 18000 marketable units, 90000 single dose containers

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PRODUCTS

ELKOFAST® gel 0.3%

Classification: class IIb Medical Device (CE_{0373} mark certification valid until Feb 2023)
Non sterile product
Visual aspect: gel formulation with viscosity of 50000-190000 cP
Product presentation: strip of sterile, gamma irradiated 3 ml LDPE UDV (5 UDV/strip). Each strip is enclosed in aluminium
Single dose container of 2.0 g of liquid formulation
Product shelf life: 24 months for storage between 4°C and 25°C

PRODUCTS

VULNOLIGHT®

Classification: class IIa Medical Device (CE0123 mark certification valid until Feb 2019)

Proprietary light source, obtained in Own Brand Labeling (OBL)

Competitive advantages if compared to the LASER source:

- **Less safety risks** (VULNOLIGHT® is classified as free from optical risks according to ISO 62471).
- **Greater treatable surface** with the same fluency.
- **Easier to use** (VULNOLIGHT® can be operated by all health personnel).
- **Significant cost reduction** about 8-10 time at full capacity

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VULNOFAST® CLINICAL STUDIES

Pre- CE mark registration phase

1. First in Human Study or Phase 1 in healthy volunteers at single dose:
   endpoints: safety and tolerability

2. Phase 2a study (Proof of concept study) in 62 diabetic patients with infected foot ulcers:
   *endpoints: efficacy safety and tolerability of a single single, topical dose of VULNOFAST® (0.1%, 0.3%, 0.5% w/w) after photoactivation with red light compared to placebo, in patients with type 1 or type 2 diabetes with infected grade 2 foot ulcers.**

*** Mannucci E. *et al. Acta Diabetol. 2014***

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VULNOFAST® Clinical experiences in progress

Update 2017

Post CE mark registration iter, i.e. market access phase:

1. in diabetic patients with foot ulcers (DFUs)
   two centers in Italy (52 patients) and Germany (11 patients)

2. in patients with infected venous and mixed leg ulcers before skin grafting (one center in Italy, 36 patients)

Evaluation of the overall bacterial burden
Evaluation of lesion surface area as a healing indicator

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WHAT MOLTENI THERAPEUTICS IS LOOKING FOR?

- MT is seeking an **out-licensing partner** for the VULNOFAST® products.
- The goal is to create a business partnership for the late development and trade:
  - Products are already available for the market.
- MT is open to evaluate a win-win partnership deal

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„Thank you for your ATTENTION"

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