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(54) Benevnelse **TRANSDERMAL THERAPEUTIC SYSTEM FOR 5-AMINOLEVULINIC ACID HYDROCHLORIDE**

(56) Anførte publikasjoner

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The present invention relates to a transdermal therapeutic system and a transdermal active ingredient-containing plaster for 5-aminolevulinic acid hydrochloride. It also relates to such a system for use in photodynamic diagnostics and therapy.

Transdermal therapeutic systems have become widespread nowadays as a form of administration for treating numerous diseases, as they demonstrate certain advantages compared to conventional forms of administration. Thus, transdermal therapeutic systems can increase the therapeutic value of an active ingredient as they ensure a constant dispensing thereof. The advantages of transdermal therapeutic systems are also that, in comparison to ointments or creams, they can be applied to the precise area and therefore at the precise dosage. Furthermore, there is no danger of inadvertently wiping off the ointment and contaminating other locations on the skin.

A transdermal therapeutic system for releasing 5-aminolevulinic acid is known from EP 1 467 706 A1. 5-aminolevulinic acid is selectively absorbed and enriched by tumour tissue, so it only leads to an increased porphyrin formation and concentration there, while the healthy tissue remains substantially uninfluenced. The effect of the 5-aminolevulinic acid is based on the stimulation of the body's own porphyrin formation. As the porphyrin strongly fluoresces upon irradiation, the 5-aminolevulinic acid or porphyrin enrichment can be used in diseased tissue to diagnose precancerous and cancerous lesions and for the protodynamic therapy thereof. A similar system is also known from EP 1 303 267 A1. The two systems have the drawback that the 5-aminolevulinic acid permeates through human skin only comparatively poorly.

WO 96/06602 discloses stable preparations with 5-aminolevulinic acid.

Actinic keratosis is designated an early form of white skin cancer, as the latter in 10% of cases can develop within a period of 10 years into a squamous cell carcinoma of the skin (spinalioma). It is chronic damage to the horny epidermis caused by the intensive action of sunlight (UV radiation) over many years. An important treatment method for actinic keratosis is so-called photodynamic therapy. An active ingredient is firstly applied here to the affected skin region and specific light-sensitive substances, the so-called porphyrins, increasingly form in the diseased skin cells. As a result, the cells are sensitised to the subsequent treatment with light and reactive oxygen is produced (photodynamic effect), which ultimately leads to the death of the corresponding cells. Good cosmetic results can generally be achieved using the photodynamic therapy. The photodynamic therapy can furthermore be repeated virtually as often as desired if the actinic keratosis occurs again. Apart from the therapeutic effect, photodynamic therapy also offers a diagnostic use. Using special light, the regions affected by actinic keratosis and pretreated by corresponding substances can be made visible in a targeted manner. It is thus possible to recognise the actinic keratosis early and to precisely determine the size of the locations affected (photodynamic diagnostics).

The aim of the present invention is to provide a transdermal therapeutic system, which as quickly as possible releases an adequate quantity of a substance into precancerous and cancerous lesions in order to then carry out the photodynamic therapy by means of irradiation. The transdermal therapeutic system should be well tolerated by the skin, be flexible and adequately sticky, even on regions that are less well accessible, such as the nasal bone or the outer ear. Furthermore, the transdermal therapeutic system should be stable, visually unobtrusive, easy to apply and remove again.

The above aim is addressed by a transdermal therapeutic system or a transdermal active ingredient-containing plaster, which comprises a back layer

that is impermeable to an active ingredient, an active ingredient-containing polymer matrix and a protective layer that can be pulled off, and characterised in that 5-aminolevulinic acid hydrochloride is used as the active ingredient, that the basic polymer of the polymer matrix is an adhesive polyacrylate, and that the polyacrylate was obtained without across-linking agent.

The transdermal therapeutic system according to the invention with 5-aminolevulinic acid hydrochloride as the active ingredient and an adhesive polyacrylate as the basic polymer of the polymer matrix is in a position to absorb adequately large quantities of the suspended pharmaceutical agent, i.e. of the 5-aminolevulinic acid hydrochloride. There is good compatibility between the adhesive polyacrylate used and the 5-aminolevulinic acid hydrochloride. The release rate of the 5-aminolevulinic acid hydrochloride during the application period is extraordinarily high. Furthermore, the transdermal therapeutic system according to the invention adheres adequately to the skin but does not irritate it. The transdermal therapeutic system according to the invention can easily be applied, especially also to small skin regions, such as the forehead, the outer ear or the nose.

The transdermal therapeutic system according to the invention is characterised in that it is capable, within about four hours, preferably within about an hour and especially preferably within about thirty minutes, of releasing a quantity of at least 3 mg 5-aminolevulinic acid hydrochloride (measured as 5-aminolevulinic acid with the so-called “paddle over disc” method, as described in European Pharmacopoeia 6.0, 2.9.4 “dissolution test for transdermal patches”, 01/2008: 20904; see also Example 4).

The transdermal therapeutic system according to the invention is preferably a monolithic active ingredient-in-adhesive system (monolithic drug-in-adhesive system). 5-aminolevulinic acid hydrochloride is suspended or dispersed directly

in the polymer matrix here. The polymer matrix carries out the three functions of the active ingredient reservoir, the control element and the adhesive layer in this case. A system of this type consists only of a back layer that is impermeable to an active ingredient, an active ingredient-containing polymer matrix and a protective layer that can be pulled off. The polymer matrix influences the adhesion to the skin, the storage of the 5-aminolevulinic acid hydrochloride and its release. A system of this type leads to a plurality of advantages during the release of hydrophilic substances, such as 5-aminolevulinic acid hydrochloride. Thus, further hydrophilic matrix materials can be avoided, so the microbiological stability is improved. The stability of the active ingredient is also increased as it is chemically inactivated. It is furthermore possible to control the release of the active ingredient by means of the particle size.

The back layer that is impermeable to the active ingredient is preferably inert and as flexible as possible, so the transdermal therapeutic system can also be applied to irregular skin regions. Any suitable material, such as, for example, polyethylene terephthalate, polyethylene, polybutylene, polyurethane, polyester, etc., can be used for the back layer. The back layer that is impermeable to an active ingredient is preferably an optionally aluminised polyester film, especially preferably a laminate made of pigmented polyethylene with aluminium vapour-coated polyester, which (provide) protection against light irradiation and therefore prevent photosensitisation before the actual photodynamic therapy.

The protective layer that can be pulled off can be produced from various materials, such as, for example, polyethylene terephthalate, polyethylene or polypropylene and is specially treated on the side in contact with the active ingredient-containing polymer matrix in order to make it as easy as possible to remove therefrom. The protective layer that can be pulled off is advantageously a polyethylene terephthalate layer.

In a preferred embodiment, the active ingredient 5-aminolevulinic acid hydrochloride is present as a crystalline 5-aminolevulinic acid hydrochloride. This has the advantage that the solubility of the active ingredient in the matrix does not have to be adjusted. Furthermore, an over-saturation and a constant diffusion pressure are thereby achieved.

In a preferred embodiment, about 50% of the crystals or particles of the crystalline 5-aminolevulinic acid hydrochloride are greater than the layer thickness of the polymer matrix. The active ingredient projects, so to speak, from the matrix, which has the advantage that on contact with the skin, especially with sweat, the projecting crystals very quickly dissolve and can therefore be easily and quickly transdermally absorbed.

More than 99.9% of the crystals of the crystalline 5-aminolevulinic acid hydrochloride are preferably smaller than about 250 µm. Although as the crystal size becomes larger, the epidermal flow increases, crystals that are too large, i.e. crystal sizes above about 250 µm, lead to clumping and streak formation.

On the other hand, it is preferred for the quantity of crystals, which are smaller than 90 µm, to make up at most 50%, and the quantity of crystals, which are smaller than 50 µm, to make up at most 25%, of the active ingredient mass, as this ensures a high active ingredient flow.

A transdermal therapeutic system with 5-aminolevulinic acid hydrochloride crystals of a particle size of 90 to 160 µm exhibits a clearly improved transepidermal flow compared with a system with particles having a particle size of less than 90 µm. This is probably because more active ingredient is released and is therefore available for the permeation. Particle sizes in the range from 90 to 160 µm are therefore especially preferred.

The polymer matrix of the transdermal therapeutic system according to the invention preferably contains less than 30 % by weight, preferably less than 20 % by weight and especially preferably less than 5 % by weight of plasticiser, for example citric acid esters, such as acetyl tributyl citrate, in relation to polyacrylate. The plasticiser content in the transdermal therapeutic system according to the invention is quite especially preferably below 5000 ppm.

So-called enhancers or permeation promoters can also preferably be dispensed with.

The adhesive polyacrylate is obtained without cross-linking agents (cross-linkers), such as, for example, aluminium acetylacetonate, polybutyl titanate or t-amyl peroxy pyrolate, etc.

The adhesive polyacrylate preferably has acid functionalities (carboxyl groups), as they are advantageous in relation to the adhesion. These are especially important when the crystals of the crystalline 5-aminolevulinic acid hydrochloride are larger than the layer thickness of the polymer matrix as whole-area contact between the transdermal therapeutic system and the skin is not then ensured. The adhesive polyacrylate with acid functionalities can, for example, be obtained by polymerisation of a monomer mixture containing an unsaturated carboxylic acid, such as, for example, acrylic acid, methacrylic acid or maleic acid.

The monomer mixtures used to produce the adhesive polyacrylates can also contain acrylic acid derivatives with epoxy groups, such as, for example, glycidyl (meth)acrylate.

The polyacrylate is preferably based on acrylic esters, such as, for example, 2-ethylhexyl acrylate. This is preferably used in a quantity of more than 50 % by

weight, especially more than 60 % by weight and especially preferably in a quantity of more than 70 % by weight, based on polyacrylate.

The viscosity of the polyacrylate is preferably in the range from 500 to 25,000, especially preferably in the range from 1,000 to 20,000 and quite especially preferably in the range from 1,500 to 12,000 mPa.s at 25°C.

In a preferred embodiment, the adhesive polyacrylate is polyacrylate based on acrylic acid, butyl acrylate, 2-ethylhexyl acrylate and vinyl acetate, based on 2-ethylhexyl acrylate, 2-hydroxyethyl acrylate and vinyl acetate, based on acrylic acid, 2-ethylhexyl acrylate and methyl acrylate, based on acrylic acid, 2-ethylhexyl acrylate and vinyl acetate, based on 2-ethylhexyl acrylate, 2-hydroxyethyl acrylate and methyl acrylate, based on 2-ethylhexyl acrylate, 2-hydroxyethyl acrylate and methyl acrylate, based on acrylic acid, butyl acrylate, 2-ethylhexyl acrylate, vinyl acetate, 2-hydroxyethyl acrylate and methyl methacrylate, based on acrylic acid, butyl acrylate, 2-ethylhexyl acrylate, vinyl acetate, *t*-octylacrylamide and vinyl acetate and based on 2-ethylhexyl acrylate and vinyl acetate.

Adhesive acrylates based on acrylic acid, butyl acrylate, 2-ethylhexyl acrylate and vinyl acetate and adhesive polyacrylates based on acrylic acid, 2-ethylhexyl acrylate and methyl acrylate, the latter supplying the best results, are especially preferred.

The adhesive polyacrylate mentioned first based on acrylic acid, butyl acrylate, 2-ethylhexyl acrylate and vinyl acetate is preferably produced from a monomer mixture, which contains 1 to 10 % by weight, preferably 3 to 7 % by weight and especially preferably about 5 % by weight acrylic acid, 5 to 25 % by weight, preferably 10 to 20 % by weight, and especially preferably about 15 % by weight butyl acrylate, 60 to 80 % by weight, preferably 70 to 78 % by weight, and

especially preferably about 75 % by weight 2-ethylhexyl acrylate and 1 to 10 % by weight, preferably 2 to 8 % by weight, and especially preferably about 5 % by weight vinyl acetate.

The adhesive polyacrylate based on acrylic acid, 2-ethylhexyl acrylate and methyl acrylate are preferably produced from a monomer mixture, which contains 1 to 10 % by weight, preferably 2 to 8 % by weight, and especially preferably about 5.7 % by weight acrylic acid, 50 to 70 % by weight, preferably 55 to 65 % by weight, and especially preferably about 62.2 % by weight 2-ethylhexyl acrylate and 20 to 40 % by weight, preferably 30 to 35 % by weight, and especially preferably about 32 % by weight methyl acrylate. In the case of the latter, small quantities of glycidyl methacrylate, for example less than 1 % by weight, preferably less than 0.05 % by weight, and especially preferably about 0.03 % by weight, glycidyl methacrylate can also be present.

In a preferred embodiment, the polymer matrix of the transdermal therapeutic system according to the invention contains more than 10 % by weight and especially preferably more than 20 % by weight 5-aminolevulinic acid hydrochloride. It was experimentally established that the release of the 5-aminolevulinic acid hydrochloride increases within the first hour, by increasing the active ingredient quantity from 20 % by weight to 30 % by weight, by about a factor of 6.

On the other hand, quantities of 5-aminolevulinic acid hydrochloride that are too large lead to a deterioration in the ability to adhere to the skin and to problems in the coating. It is therefore preferred if less than 35 % by weight and especially less than 30 % by weight 5-aminolevulinic acid hydrochloride is present. The range between 25 and 30 % by weight is optimal.

The quantity of the polyacrylate used in the transdermal therapeutic system according to the invention is preferably more than 60 % by weight and especially preferably more than 70 % by weight.

In a preferred embodiment, the transdermal therapeutic system is a monolithic active ingredient-in-adhesive system, more than 99.9 % of the crystals of the crystalline 5-aminolevulinic acid hydrochloride are smaller than 250 µm, the adhesive polyacrylate is based on acrylic acid, butyl acrylate, 2-ethylhexyl acrylate and vinyl acetate and especially preferably on acrylic acid, 2-ethylhexyl acrylate and methyl acrylate, and the polymer matrix contains 25 to 30 % by weight, preferably about 28 % by weight, 5-aminolevulinic acid hydrochloride and 70 or more % by weight, preferably about 72 % by weight, polyacrylate. A system of this type exhibits a very rapid release of a large quantity of active ingredient and the processability is excellent.

The transdermal therapeutic system according to the invention is produced in a known manner. An active ingredient-containing adhesive mass based on an adhesive polyacrylate is firstly produced. Ethanol, ethyl acetate, heptane, hexane, isopropyl alcohol, methanol, toluene, 2,4-pentandiene and mixtures thereof are preferably possible solvents. Ethyl acetate and hexane are especially preferred. Conventional coating, drying and laminating methods and cutting follow. The solvent is almost completely removed during the drying process. Perforation and packaging finally follow.

The present invention also relates to the transdermal therapeutic system according to the invention for use in the diagnosis and therapy of preliminary skin cancer stages, such as actinic keratosis, and of skin cancer and oncological skin diseases. The external application of the transdermal therapeutic system leads to the penetration and enrichment of the active ingredient in the diseased tissue. 5-aminolevulinic acid hydrochloride is an endogenous compound and a precursor

substance in the biosynthesis of porphyrins, which are constituents, for example, of the haemoglobin and the cytochrome cycle. 5-aminolevulinic acid hydrochloride is converted into the actual photosensitiser, the protoporphyrin IX (PPIX). After the enrichment, an irradiation takes place with adequate light, for example with light of various wavelengths, such as, for example, 408 mm, 506 mm, 532 mm, 580 mm and 635 mm. In this case, reactive oxygen compounds are produced, which make the target tissue visible during the diagnosis or lead to an apoptosis and necrosis thereof during the therapy.

The present invention also relates to a transdermal therapeutic system, as described above, for use as a therapeutic agent.

Furthermore, a transdermal therapeutic system, as described above, is disclosed for treating preliminary skin cancer stages, such as, for example, actinic keratosis, and oncological skin diseases. The transdermal therapeutic system can be used to treat actinic keratosis.

Examples

Example 1

The transdermal therapeutic system produced contains the following constituents:

		% (% by weight/% by weight)	mg/Plaster
Active ingredient:	5-aminolevulinic acid hydrochloride	19.7	10.2
Polymer [a)] :	DURO-TAK 387-2353	49.6	25.8
Back layer:	3M ScotchPak	30.7	16.0

	1109		
Protective layer:	polyethylene terephthalate layer siliconised on one side (75 µm)	[b]	59.0 [c]

[a] in ethyl acetate and hexane, which are both virtually completely removed during the drying process

[b] is removed before application

[c] estimated

In relation to the polymer matrix, 28 % by weight 5-aminolevulinic acid hydrochloride and 72 % by weight DURO-TAK 387-2353 (polyacrylate without cross-linking agent) are accordingly present.

Example 2 (not according to the invention)

The composition of this example corresponds to Example 1, except that instead of DURO-TAK 387-2353, the same quantity of DURO-TAK 387-2052 (polyacrylate with cross-linking agent) was used.

Comparative Example 3

The composition of this example corresponds to Example 1, except that instead of DURO-TAK 387-2353, the same quantity of Bio-PSA 4301 (a silicone polymer) was used.

Example 4

The release rate was measured using the so-called “paddle over disc” method, as described in European Pharmacopoeia 6.0, 2.9.4. “dissolution test for transdermal patches”, 01/2008 : 20904, under the following conditions:

Apparatus used:	paddle over disc
Release medium:	citrate buffer pH 3.0
Volume of the release medium:	300 ml
Temperature:	32°C ± 0.5°C
Rotation frequency:	50 min^{-1}
Sample removal time:	0.5 h, 2 h and 7 h
Sample volume:	10.0 ml

The results are shown in Fig. 1.

The release rate of a transdermal therapeutic system according to Example 1 is higher than that according to Example 2. Both Example 1 and Example 2 exhibit a clearly faster release compared to comparative Example 3. Furthermore, the stability of the 5-aminolevulinic acid hydrochloride according to Example 1 after one and three months is higher than that of the 5-aminolevulinic acid hydrochloride according to Example 2, which is degraded more quickly.

Patentkrav

1. Transdermalt terapeutisk system, omfattende et virkestoffgjennomtrengelig bakre lag, en virkestoffholdig polymermatriks og et avtrekkbart beskyttelseslag, **karakterisert ved at** virkestoffet er 5-aminolevulinsyrehydroklorid, at basispolymeren i polymermatriksen er et adhesjonsklebende polyakrylat, og at polyakrylatet ble oppnådd uten fornettingsmiddel.

2. Transdermalt terapeutisk system ifølge krav 1, **karakterisert ved at** det transdermale terapeutiske systemet er et monolittisk virkestoff-i-klebestoff-system.

3. Transdermalt terapeutisk system ifølge minst ett av de foregående kravene, **karakterisert ved at** 5-aminolevulinsyrehydrokloridet er krystallinsk 5-aminolevulinsyrehydroklorid.

4. Transdermalt terapeutisk system ifølge minst ett av de foregående kravene, **karakterisert ved at** 50 % av krystallene i det krystallinske 5-aminolevulinsyrehydrokloridet er større en polymermatriksens lagtykkelse.

5. Transdermalt terapeutisk system ifølge minst ett av de foregående kravene, **karakterisert ved at** mer enn 99,9 % av krystallene i det krystallinske 5-aminolevulinsyrehydrokloridet er mindre enn omtrent 250 µm og har spesielt foretrukket en partikkelstørrelse på 90 til 160 µm.

6. Transdermalt terapeutisk system ifølge minst ett av de foregående kravene, **karakterisert ved at** polymermatriksen inneholder mindre enn 30 vekt-%, foretrukket mindre enn 20 vekt-% og spesielt mindre enn 5 vekt-% mykgjøringsmiddel, i forhold til polyakrylatet.

7. Transdermalt terapeutisk system ifølge minst ett av de foregående kravene, **karakterisert ved at** polyakrylatet har syrefunksjonaliteter.

8. Transdermalt terapeutisk system ifølge minst ett av de foregående kravene, **karakterisert ved at** polyakrylatet er et polyakrylat basert på akrylsyre, butylakrylat, 2-etylheksylakrylat og vinylacetat eller basert på akrylsyre, 2-etylheksylakrylat og metylakrylat.

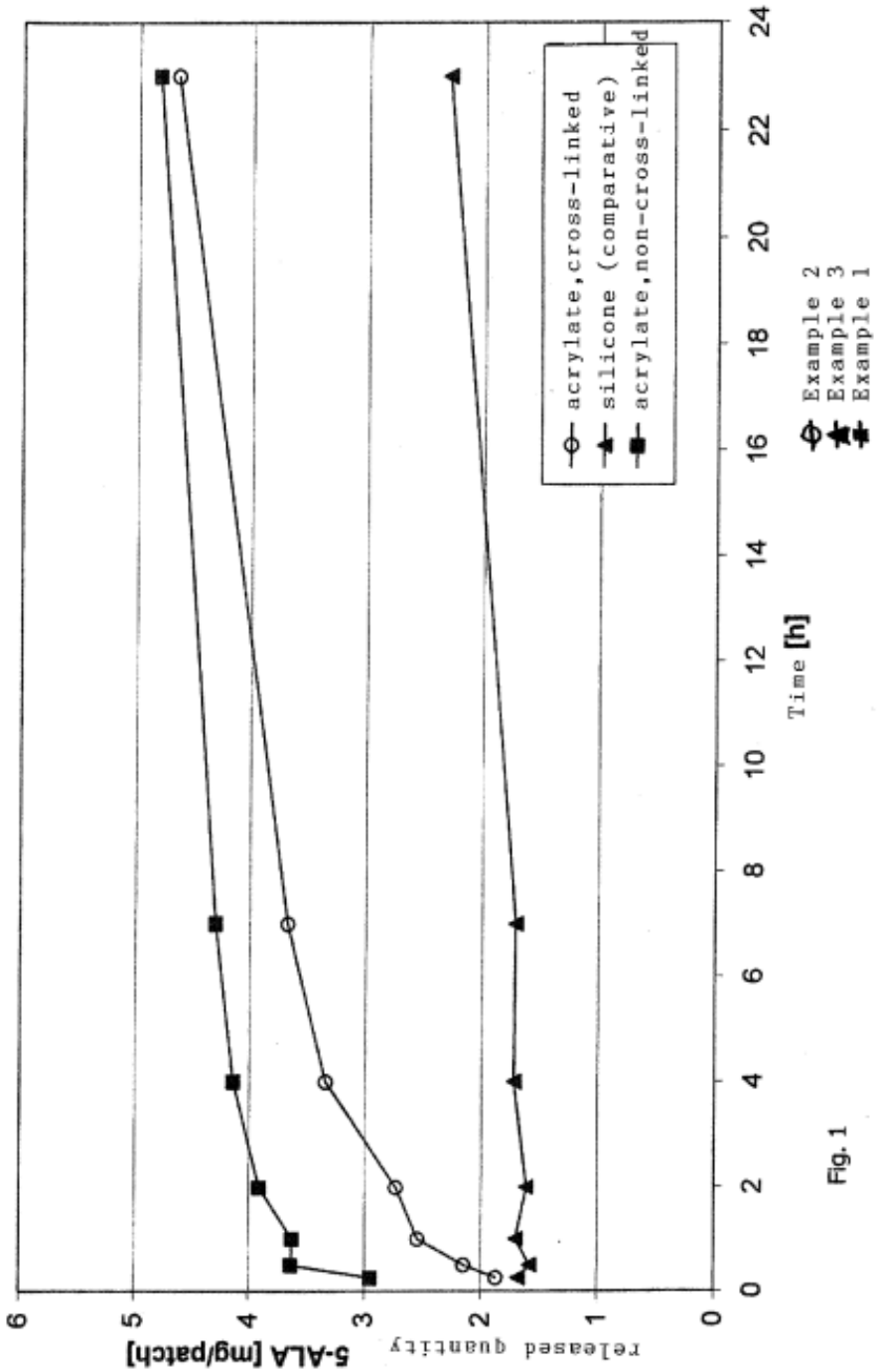
9. Transdermalt terapeutisk system ifølge minst ett av de foregående kravene, **karakterisert ved at** polymermatriksen inneholder mer enn 10 vekt-%, foretrukket mer enn 20 vekt-% og spesielt foretrukket 25 til 30 vekt-% 5-aminolevulinsyrehydroklorid.

10. Transdermalt terapeutisk system ifølge minst ett av de foregående kravene, **karakterisert ved at** polymermatriksen inneholder mer enn 60 vekt-%, polyakrylat, foretrukket mer enn 65 vekt-% og spesielt foretrukket mer enn 70 vekt-% polyakrylat.

11. Transdermalt terapeutisk system ifølge minst ett av de foregående kravene, **karakterisert ved at** det transdermale terapeutiske systemet er et monolittisk virkestoff-i-klebestoff-system, og at polymermatriksen inneholder omtrent 28 vekt-% krystallinsk 5-aminolevulinsyrehydroklorid og omtrent 72 vekt-% polyakrylat basert på akrylsyre, 2-etylheksylakrylat og metylakrylat som ble oppnådd uten fornettingsmiddel.

12. Transdermalt terapeutisk system ifølge minst ett av de foregående kravene for anvendelse som terapeutisk middel.

13. Transdermalt terapeutisk system ifølge et av kravene 1 til 12 for anvendelse ved diagnose og behandling av hudkreftforstadier, som for eksempel aktinisk keratose, og onkologiske hudsykdommer.


5-ALA [mg/patch]
released quantity
Time [h]
acrylate,cross-linked
silicone (comparative)
acrylate,non-cross-linked
Example 2
Example 3
Example 1
0
1
2
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8
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Fig. 1