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**Utilization of powder preparations containing hydroxypyridones for treating leg
ulcers and decubitus ulcers**

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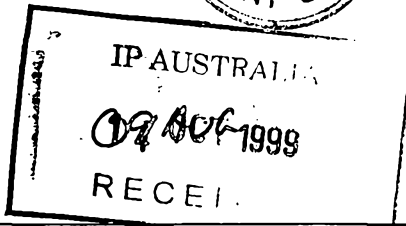
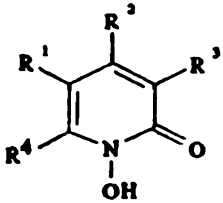
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**PCT**WELTORGANISATION FÜR GEISTIGES EIGENTUM
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| (54) Title: UTILIZATION OF POWDER PREPARATIONS CONTAINING HYDROXYPYRIDONES FOR TREATING LEG ULCERS AND DECUBITUS ULCERS | | | |
| (54) Bezeichnung: VERWENDUNG VON HYDROXYPYRIDON-HALTIGEN PUDERZUBEREITUNGEN ZUR BEHANDLUNG VON UNTERSCHENKEL- UND DRUCKGESCHWÜREN | | | |
| <div style="text-align: center;">  <p>(I)</p> </div> | | | |
| (57) Abstract | | | |
| The inventive powder preparations containing at least one compound of formula (I) are suited for treating leg ulcers or decubitus ulcers. | | | |
| (57) Zusammenfassung | | | |
| Puderzubereitungen, enthaltend mindestens eine Verbindung der Formel (I), eignen sich zur Behandlung von Unterschenkelgeschwüren oder Dekubitalulzera. | | | |

THE USE OF HYDROXYPYRIDONE-CONTAINING POWDER PREPARATIONS
FOR THE TREATMENT OF LEG ULCERS AND PRESSURE ULCERS

The present invention relates to the use of a powder preparation containing hydroxypyridones for the treatment of leg ulcers (ulcus cruris) and
5 pressure ulcers (decubitus ulcers).

The diagnosis of leg ulcers (ulcus cruris) is a collective term covering ulcers of varying origins (Phlebologie (1996); 25:254-258). In Germany, about 1.6 million people are affected by poorly healing leg ulcers. The prerequisite for effective treatment of leg ulcer wounds is to identify the possible causes of the
10 development of the defect. It is possible to make the global statement of blood flow in the vessels of the lower leg is disturbed. The under-supply of the tissue with oxygen resulting from this leads to lesions, loss of tissue and finally necrosis and expansion of the defect. Infections with bacteria and fungi colonize the affected areas of skin and, in addition to enlarging the wound, also contribute to
15 the formation of a very malodorous discharge.

The therapy of leg ulcers consists of a dual strategy of local wound treatment and elimination of the causes of the ulceration. The latter may include compression therapy of an ulcer caused by chronic venous hypertension as well as rehabilitation of the arterial system for arterial leg ulcers.

It must always be taken into account in principle during local therapy of an ulcer that polypharmacy in use of the agents is avoided where possible because the patients often have multivalent contact allergies, in particular to ingredients of the local therapy which is sometimes applied to them for some years. The composition of local therapeutic agents should therefore be as simple as possible
20 and the number of substances used should be kept as small as possible.

At present 2 treatment methods are accepted for local ulcer therapy, namely a phase-adapted and a phase-overlapping wound treatment.



These therapeutic policies relate to the 3 phases of wound healing, which take place as follows:

- Exudation phase
(frequently triggered by superinfection of the ulcer)
- Granulation phase
- Epithelization phase

Phase-adapted wound healing corresponds to the conventional, traditional therapy, must be continually changed and is elaborate but low-cost. Phase-overlapping therapy, which makes use of modern wound dressings with which treatment in the same way is possible in all 3 phases, is considerably simpler to manage but also considerably more costly. The two methods of therapy are comparable to one another in the therapeutic effect.

Phase-adapted wound treatment intervenes in the 3 phases of wound healing as follows:

- Cleansing
- Promotion of granulation
- Promotion of epithelization through drying out

The aim of cleansing is to produce a clean floor of the wound. For this it is necessary firstly to remove ointment residues and scabs and cut away any necroses present. The latter is best performed with a sharp spoon and with forceps and scissors. It is also possible to use enzymatic ointments which preferably degrade denatured protein. They contain substances such as trypsin, chymotrypsin, collagenase, fibrolysin, streptokinase etc. The surroundings of the ulcers should always be protected by applying hard zinc paste during this. Regular disinfection takes place in parallel with this, for example with potassium permanganate or Rivanol[®] baths.

Use of local antibiotics should be avoided because, on the one hand, resistance development and, on the other hand, the rate of sensitization is high.



Granulation is promoted by mechanical stimulation. This is why curettage with a sharp spoon is still a very successful remedy. Somewhat milder stimulation of the floor of the wound is possible with sea sand, crystallized sugar or dextran powder. Hypertonic glucose and sodium chloride solutions also
5 promote granulation. The treatments which were formerly customary with ointments, dyes and refined mineral oils are no longer recommended because on prolonged use they frequently lead to contact allergies.

The aim in the epithelization phase is to protect the sensitive newly formed tissue and promote epithelization. Epithelization starts when the granulation
10 tissue has reached the upper level of the skin. Suitable as epithelization-promoting wound dressing are a number of products, for example hydrogels, hydrocolloids, foam compresses and gauze lattices. Transplantation of split skin can also be performed.

In phase-overlapping wound treatment for example dry wound dressings
15 and gels (xerodressing and xerogel), and hydrocolloid wound dressings (hydrocolloid dressings) are used. They display their effect in each phase and can be employed as monotherapy for the treatment of leg ulcers. Their properties include exudate retention, ulcer cleansing and promotion of granulation and epithelization.

20 According to publications from England, Denmark, Canada, Sweden, South Africa and the USA, 1 to 11% of all patients in hospitals had pressure ulcers: the causation of this involves increasing life expectancy, the increase in patients at risk, and the fact that increasing numbers of extremely ill and seriously injured patients survive. Additional factors are the increasing shortage of nursing
25 staff and the continuous overwork thereof.

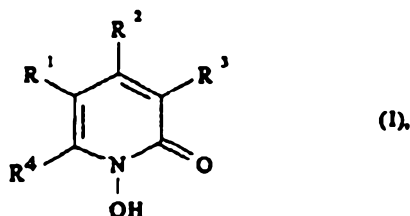
Pressure maintained for a lengthy period on the skin with a disturbance of the microcirculation is the most important factor leading to a pressure ulcer (National Pressure Ulcer Advisory Panel (1989)). An important part is also played by shear forces acting on the skin and the underlying tissue, and friction and
30 moisture. A decrease in patient mobility means more long-lasting stress on the skin at the same point. In the supine position, this is particularly the sacral region of the skin. Patients at particular risk of



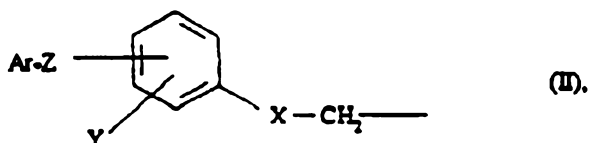
pressure ulcers are therefore elderly ones who are immobile, whose blood flow is impaired or who suffer from neurological disorders. Besides relieving the pressure on the affected areas of skin, the local treatment of decubitus ulcers is carried out in principle in the same way as for leg ulcers.

It has now been found that powder preparations of hydroxypyridone derivatives are extremely suitable for simple and cost-effective phase-overlapping local therapy of leg ulcers and pressure ulcers. This finding is surprising inasmuch as hydroxypyridone-containing preparations have to date been used exclusively as antimicrobial agents.

The invention therefore relates to the use of powder and at least one compound of the formula I



in which R^1 , R^2 and R^3 , which are identical or different, are hydrogen atom or alkyl with 1-4 carbon atoms, and R^4 is a saturated hydrocarbon radical with 6 to 9 carbon atoms or a radical of the formula II



where

X is S or O,

Y is hydrogen atom or up to 2 halogen atoms such as chlorine and/or bromine,

Z is a single bond or the divalent radicals O, S, $-CR_2-$, in which R is hydrogen or C_1-C_4 -alkyl, or other divalent radicals with 2-10 C and, where appropriate, O and/or S atoms linked in the form of a chain, it



being necessary – if the radicals contain 2 or more O and/or S atoms – for the latter to be separated from one another by at least 2 C atoms, and it also being possible for 2 adjacent C atoms to be linked together by a double bond, and the free valencies of the C atoms being saturated by H and/or C₁-C₄-alkyl groups,

Ar is an aromatic ring system which has up to two rings and which may be substituted by up to three radicals from the group of fluorine, chlorine, bromine, methoxy, C₁-C₄-alkyl, trifluoromethyl and trifluoromethoxy, for the production of a pharmaceutical for the treatment of leg ulcers and/or pressure ulcers.

The term "saturated hydrocarbon radical" means that the radical can be straight-chain, branched or cyclic and contains no aliphatic multiple bonds. Examples of the R⁴ radical are hexyl, heptyl, octyl, cyclohexyl or cycloheptyl.

The hydrocarbon radical R⁴ in the compound of the formula I is preferably C₆-C₈-alkyl or cyclohexyl, which may also be linked via a methylene or ethylene group to the pyridone ring or may contain an endo-methyl group. R⁴ may also be an aromatic radical which, however, is preferably linked via at least one aliphatic C atom to the pyridone residue.

The C chain members in the "Z" radicals are preferably CH₂ groups. If the CH₂ groups are substituted by (C₁-C₄)-alkyl groups, the preferred substituents are CH₃ and C₂H₅.

Examples of "Z" radicals are:

-O-, -S-, -CH₂-, -(CH₂)_m- (m=2-10), -C(CH₃)₂-, -CH₂O-, OCH₂-, -CH₂S-, -SCH₂-, -SCH(C₂H₅)-, -CH=CH-CH₂O-, -OCH₂CH=CHCH₂O-, -OCH₂CH₂O-, -OCH₂CH₂CH₂O-, -SCH₂CH₂CH₂S-, SCH₂CH₂CH₂CH₂O-, -SCH₂CH₂OCH₂CH₂O-, -SCH₂CH₂OCH₂CH₂OCH₂CH₂S- or -SCH₂C(CH₃)₂CH₂S-.

The "S" radical means a sulfur atom, and the "O" radical means an oxygen atom. The term "Ar" means phenyl and condensed systems such as naphthyl, tetrahydronaphthyl and indenyl, and isolated systems like those derived from biphenyl, diphenylalkanes, diphenyl ethers and diphenyl



thioethers. The term "alkyl with 1 to 4 carbon atoms" means radicals such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or tertiary butyl.

Important representatives of the class of compounds characterized by formula I are:

6-[4-(4-chlorophenoxy)phenoxyethyl]-1-hydroxy-4-methyl-2-pyridone;

6-[4-(2,4-dichlorophenoxy)phenoxyethyl]-1-hydroxy-4-methyl-2-pyridone;

6-(biphenyl-4-oxymethyl)-1-hydroxy-4-methyl-2-pyridone;

6-(4-benzylphenoxyethyl)-1-hydroxy-4-methyl-2-pyridone;

6-[4-(2,4-dichlorobenzoyloxy)phenoxyethyl]-1-hydroxy-4-methyl-2-pyridone;

6-[4-(4-chlorophenoxy)phenoxyethyl]-1-hydroxy-3,4-dimethyl-2-pyridone;

6-[4-(2,4-dichlorobenzyl)phenoxyethyl]-1-hydroxy-3,4-dimethyl-2-pyridone;

6-[4-(cinnamoyloxy)phenoxyethyl]-1-hydroxy-4-methyl-2-pyridone;

1-hydroxy-4-methyl-6-[4-(4-trifluoromethylphenoxy)phenoxyethyl]-2-pyridone;

1-hydroxy-4-methyl-6-cyclohexyl-2-pyridone;

1-hydroxy-4-methyl-6-(2,4,4-trimethylpentyl)-2-pyridone,

1-hydroxy-4-methyl-6-n-hexyl-, -6-iso-hexyl-, 6-n-heptyl- or -6-isoheptyl-2-pyridone, 1-hydroxy-4-methyl-6-octyl- or -6-isooctyl-2-pyridone, in particular 1-hydroxy-4-methyl-6-cyclohexylethyl- or 6-cyclohexylethyl-2-pyridone, it being possible for the cyclohexyl radical in each case also to carry a methyl radical,

1-hydroxy-4-methyl-6-(2-bicyclo[2,2,1]heptyl)-2-pyridone, 1-hydroxy-3,4-dimethyl-6-benzyl- or -6-dimethylbenzyl-2-pyridone or 1-hydroxy-4-methyl-6-(β -phenylethyl)-2-pyridone.

The abovementioned compounds of the formula I can be employed both in free form and in the form of salts; the use in free form is preferred.

The active ingredients of the compound of the formula I to be employed in the preparations can be prepared, for example, by processes disclosed in US 2 540 218 or US 4 797 409.

Powder preparations are particularly suitable for the use according to the invention of said compounds.



The active ingredient is incorporated into the preparations according to the invention in amounts which are normally between about 0.05 and about 5%, preferably between 0.1 and 1%.

It is possible with the pharmaceuticals according to the invention to achieve a thorough cure on local treatment of leg ulcers and decubitus ulcers.

Suitable as powder base are native substances such as sucrose, lactose, gelatin, pectin, carrageenan, agar, tragacanth and alginates, semisynthetic powder bases such as cellulose ethers, derivatives of starch, dextran and pectin, and completely synthetic substances such as polyvinylpyrrolidones. Modified starch types are particularly suitable. They are employed in amounts of from 95.0 to 99.4 parts by weight per 100 parts by weight of final product.

A further excipient suitable for the pharmaceutical preparation according to the invention is highly disperse silica to improve the flow and dusting properties.

The preparations are produced in a manner known per se by mixing the individual components and - where necessary - further processing adapted to the particular preparation.

The present invention is explained in detail by the following examples but is not confined to these. Unless otherwise noted, the stated amounts are based on weight.

Example 1

A preparation according to the invention has the following composition:

| | |
|---|---------|
| 6-Cyclohexyl-1-hydroxy-4-methyl-2(1H)-pyridone, | 1.00 g |
| 2-aminoethanol set | |
| Highly disperse silica | 0.01 g |
| Modified corn starch, phosphated | 98.99 g |

Example 2

A preparation according to the invention has the following composition:



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| | |
|--|---------|
| 1-Hydroxy-4-methyl-6-(2,4,4-trimethylpentyl)-2(1H)pyridone | 0.50 g |
| Sucrose | 99.50 g |

Example 3

- 5 A preparation according to the invention has the following composition:

| | |
|---|---------|
| 6-[4-(4-Chlorophenoxy)phenoxyethyl]-1-hydroxy-4-methyl-2(1H)-pyridone | 0.25 g |
| Lactose | 99.75 g |

10

Example 4

Activity test

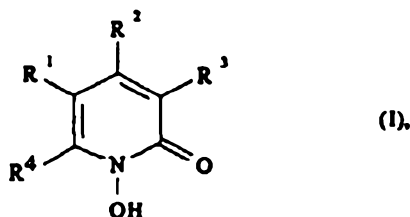
- It was possible to show in a clinical study on patients with poorly healing leg ulcers that the ulcer area decreased by 80% after a treatment period of 6 weeks with the preparation according to Example 1 according to the invention. By comparison with this, the size of the wound decreased by only about 30% after standard therapy (hydrogen peroxide, potassium permanganate, sodium chloride solution).

- 20 "Comprises/comprising" when used in this specification is taken to specify the presence of stated features, integers, steps or components but does not preclude the presence or addition of one or more other features, integers, steps, components or groups thereof.



Patent claims:

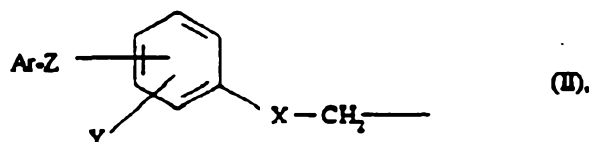
1. The use of powder and at least one 1-hydroxy-2-pyridone of the formula I



where

R^1 , R^2 and R^3 , which are identical or different, are hydrogen atom or alkyl with 1-4 carbon atoms, and

R^4 is a saturated hydrocarbon radical with 6 to 9 carbon atoms or a radical of the formula II



where

X is S or O,

Y is hydrogen atom or up to 2 halogen atoms such as chlorine and/or bromine,

Z is a single bond or the divalent radicals O, S, $-CR_2-$, in which R is hydrogen or (C_1-C_4) -alkyl, or other divalent radicals with 2-10 C and, where appropriate, O and/or S atoms linked in the form of a chain, it being necessary - if the radicals contain 2 or more O and/or S atoms - for the latter to be separated from one another by at least 2 C atoms, and it also being possible for 2 adjacent C atoms to be linked together by a double bond, and the free valencies of the C atoms being saturated by hydrogen atom and/or (C_1-C_4) -alkyl groups,

Ar is an aromatic ring system which has up to two rings and which may be substituted by up to three radicals from the group of fluorine, chlorine, bromine, methoxy, (C_1-C_4) -alkyl, trifluoromethyl



and trifluoromethoxy, for the production of a pharmaceutical for the treatment of leg ulcers and/or pressure ulcers.

2. The use as claimed in claim 1, wherein the compound of the formula I in which Ar is a bicyclic system which is derived from biphenyl, diphenylalkane or diphenyl ether is employed.

3. The use as claimed in claim 1 or 2, wherein the compound of the formula I contains a cyclohexyl radical in position R⁴.

4. The use as claimed in any one of claims 1 to 3, wherein the compound of the formula I contains an octyl radical of the formula $-\text{CH}_2\text{-CH}(\text{CH}_3)\text{-CH}_2\text{-C}(\text{CH}_3)_3$ in position R⁴.

5. The use as claimed in claim 1, wherein 1-hydroxy-4-methyl-6-[4-(4-chlorophenoxy)phenoxy-methyl]-2-(1H)pyridone, 1-hydroxy-4-methyl-6-cyclohexyl-2-(1-H)-pyridone or 1-hydroxy-4-methyl-6-(2,4,4-trimethylpentyl)-2-(1H)-pyridone is employed.

6. The use as claimed in any one of claims 1 to 5, wherein modified corn starch, sucrose, lactose or a mixture thereof is employed as powder base.

7. The use as claimed in any one of claims 1 to 6, wherein highly disperse silica is additionally employed.

8. The use as claimed in any one of claims 1 to 7, wherein the amount of 1-hydroxy-2-pyridone of the formula I used is from 0.05% to about 5%.

9. The use as claimed in any one of claims 1 to 7 wherein the amount of 1-hydroxy-2-pyridone of the formula I used is from 0.1% to 1%.



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10. A method of treatment of leg ulcers and/or pressure ulcers comprising administering to a person in need of such treatment an efficacious amount of at least one 1-hydroxy-2-pyridone of the formula I as claimed in any one of claims 1 to 4 and/or its physiologically acceptable salt.

DATED this 4th day of March 2002

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