Abstract:

This invention relates to wound-healing pharmaceutical or cosmetic (anti-skin aging) compositions in the form of a cream based on amino acids and sodium hyaluronate.
WOUND-HEALING PHARMACEUTICAL COMPOSITIONS IN THE FORM OF A CREAM BASED ON AMINO ACIDS AND SODIUM HYALURONATE

FIELD OF INVENTION

The present invention relates to wound-healing pharmaceutical compositions in the form of a cream based on amino acids and sodium hyaluronate.

PRIOR ART

In the absence of suitable preventive actions, patients who are paralysed or bedridden for long periods are liable to ischaemic necrosis and ulceration of the tissues covering projecting bones, especially in the sacral, ischial, malleolar, heel and great trochanter regions.

Bedsores and chronic ulcerous wounds are usually treated with gentle massage to restore the circulation, possibly with mechanical removal of the necrotic tissue and cleansing with soap (which can cause oedema or dehydration), or with hydrophilic polymers, hydrogen peroxide or alcohol rubs (which can cause damage because the removal of the fats in the cutaneous tissue dries and cracks the skin).

Serious burns also require debridement of the affected area and removal of necrotic tissue.

DESCRIPTION OF THE INVENTION

It has now been found that the combination of some amino acids with sodium hyaluronate is particularly effective in promoting the process of cell reintegration which forms the basis for fast wound-healing, aiding the reconstruction of connective tissue and the consequent regeneration of epithelial cells.

The invention therefore relates to wound-healing pharmaceutical
compositions in the form of a cream, containing, as active ingredient, a combination of:

- a) glycine and proline;
- b) sodium hyaluronate; and possibly;
- c) lysine and leucine.

More particularly, the compositions according to the invention contain glycine, L-proline and sodium hyaluronate, and possibly L-lysine in hydrochloride form, and L-leucine.

The compositions according to the invention have proved a surprising adjuvant effect in promoting the healing of ordinary wounds, including surgical wounds, vaginal and rectal lesions, buccal wounds and lesions, including those from dental surgery, as well as wounds which cannot be stitched and have seriously damaged the dermis, including loss of skin substance, such as chronic ulcerous wounds, serious burns and bedsores.

The compositions of the invention promote the elimination of necrotic tissue, thus facilitating more rapid regeneration of the tissues, and maintain the ideal humidity conditions to aid re-epithelialisation of the skin lesions, at the same time preventing the spread of germs.

The compositions of the invention are also useful for the treatment and/or prevention of skin aging.

The compositions of the invention will be applied to the affected area after removing any foreign material by thorough washing with a hydrogen peroxide solution or saline solution, and removing any excess blood with sterile gauze.

For the vaginal and rectal administration, the compositions of the invention will be applied to the affected area possibly after suitable cleansing of the affected area with appropriate cleansing formulations.

The compositions according to the invention will contain the various
active ingredients within the following percentage ranges by weight:

- glycine 0.5 to 2%;
- L-proline: 0.2 to 1.5%;
- sodium hyaluronate: 0.5 to 3%;

and possibly

- L-lysine hydrochloride: 0.05 to 1%;
- L-leucine: 0.05 to 0.3%.

According to a preferred aspect, the compositions according to the invention will contain the various active ingredients in the following percentages by weight:

- glycine 1%;
- L-proline: 0.75%;
- sodium hyaluronate: 1.33%;

and possibly

- L-lysine hydrochloride: 0.1%;
- L-leucine: 0.15%.

The compositions according to the invention can be formulated suitably for the topical administration in the form of a cream, and prepared according to conventional methods well known in pharmaceutical technology, such as those described in Remington's Pharmaceutical Handbook, Mack Publishing Co., N.Y., USA, using excipients, solubilisers, emollients, stabilisers, emulsifiers, pH regulators, and preservatives acceptable for their final use.

**PHARMACOLOGICAL TRIAL**

The ability of the compositions of the invention to heal chronic sores in elderly patients, diabetics and patients with vascular disease was evaluated.

In particular, 32 elderly patients suffering from bedsores, 31 Type II diabetics with ulcers extending to the lower limbs, and 38 patients with post-phlebitic ulcers were evaluated.
The treatment was given three/four times a week, depending on the severity of the lesions, by spreading the cream on the wound.

The bedsores had to have a de-epithelialised area of over 10 cm² which had already been treated by conventional means for over 4 months, without any evident results. The type of bandage was irrelevant.

The sore was clinically evaluated and photographed before treatment in the fourth and eighth weeks of the trial. "Healing" was defined as closing of the wounds, and "improvement" as a reduction in size of the treated area exceeding 70% of the initial area.

By the fourth week of treatment 20 patients showed an improvement, namely a reduction in size of the sore of over 70%, and 3 were completely healed; by the end of the observation period (8th week), 16 patients were healed, 12 had improved and 4 patients presented a reduction of under 50% in the de-epithelialised area.

Of the 31 diabetics with ulcers of various areas and depths, which had already been treated unsuccessfully for at least four months prior to our study, 9 were healed after four weeks' treatment, and another 16 no longer presented ulcerated areas by the end of treatment period. In 6 particularly serious cases there was an improvement, but the sore was still present by the end of the 8th week of treatment.

In patients with post-phlebitic ulcers who had already undergone conventional treatment for at least two months with no result, the administration of the cream compositions according to the invention led to healing within one month in 15 patients and by the end of treatment (8th week) in another 19 patients, making a total of 34 out of 38 treated.

In conclusion, in the case of bedsores, diabetic and post-phlebitic skin ulcers, the cream compositions according to the invention obtained healing indexes (expressed as % improvement) exceeding 80% by comparison with
conventional treatment.

The compositions of the invention also proved to be very effective in the treatment of ordinary wounds, including surgical wounds, vaginal and rectal lesions as well as in the treatment and/or prevention of skin aging.

The compositions of the invention also proved to be very effective in the treatment of buccal wounds and lesions, including those from dental surgery.

An example of a cream formulation according to the invention is set out below.

**EXAMPLE**

<table>
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<tr>
<th>INGREDIENTS</th>
<th>% Composition</th>
</tr>
</thead>
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<tr>
<td>Purified water</td>
<td>82.27</td>
</tr>
<tr>
<td>Sodium hyaluronate</td>
<td>1.33</td>
</tr>
<tr>
<td>Glycine</td>
<td>1.00</td>
</tr>
<tr>
<td>L-Proline</td>
<td>0.75</td>
</tr>
<tr>
<td>L-Leucine</td>
<td>0.15</td>
</tr>
<tr>
<td>L-Lysine HCl</td>
<td>0.10</td>
</tr>
<tr>
<td>Cetyl stearyl octanoate (Saboderm CSO)</td>
<td>6.00</td>
</tr>
<tr>
<td>Acrylic acid and vinyl ester copolymer (Stablen30)</td>
<td>0.30</td>
</tr>
<tr>
<td>Cetyl stearyl alcohol (Lanette O)</td>
<td>4.00</td>
</tr>
<tr>
<td>Potassium cetyl phosphate (Amphisol K)</td>
<td>3.00</td>
</tr>
<tr>
<td>Imidazolidinyl urea (Preservative G)</td>
<td>0.30</td>
</tr>
<tr>
<td>Phenoxyethanol-parabens (Sepicide Hb2)</td>
<td>0.60</td>
</tr>
<tr>
<td>32% Sodium hydroxide</td>
<td>0.20</td>
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CLAIMS

1. Topical pharmaceutical compositions in the form of a cream, containing as active ingredient a combination of:
   a) glycine and proline;
   b) sodium hyaluronate; and possibly;
   c) lysine and leucine.

2. Compositions as claimed in claim 1, containing the various active ingredients within the following percentage ranges by weight:
   - glycine 0.5 to 2%;
   - L-proline: 0.2 to 1.5%;
   - sodium hyaluronate: 0.5 to 3%;

   and possibly
   - L-lysine hydrochloride: 0.05 to 1%;
   - L-leucine: 0.05 to 0.3%.

3. Compositions as claimed in claim 2, containing the various active ingredients in the following percentages by weight:
   - glycine 1%;
   - L-proline: 0.75%;
   - sodium hyaluronate: 1.33%;

   and possibly
   - L-lysine hydrochloride: 0.1%;
   - L-leucine: 0.15%.

4. Use of combinations of
   a) glycine and proline;
   b) sodium hyaluronate; and possibly;
   c) lysine and leucine;

   for the preparation of topical medicaments in the form of a cream for the
treatment of ordinary wounds, including surgical wounds, vaginal and rectal
lesions, buccal wounds and lesions, including those from dental surgery,
chronic ulcerous wounds, serious burns, bedsores, skin aging.

5. Use of combinations of
   a) glycine and proline;
   b) sodium hyaluronate; and possibly;
   c) lysine and leucine;

for the preparation of topical medicaments in the form of a cream for the
vaginal and rectal administration.

6. Use of combinations of
   a) glycine and proline;
   b) sodium hyaluronate; and possibly;
   c) lysine and leucine;

for the preparation of topical medicaments in the form of a cream for the
buccal administration.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

INV. A61K31/198  A61K31/401  A61K31/728  A61P17/02

According to international Patent Classification (IPC) or to both national classification and IPC.

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical search terms used)

EPO-Internal , WPI Data, EMBASE, BIOSIS

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
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<td>FR 2 864 445 A1 (THOREL JEAN NOEL [FR]; GATTO HUGUES [FR]); 1 July 2005 (2005-07-01); page 3, lines 2-7; page 4; table 2; page 23, line 19 - page 24, line 29</td>
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<td>X</td>
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<td>Y</td>
<td>EP 1 161 945 A2 (SOLARTIUM ESTABLISHMENT [LI]); 12 December 2001 (2001-12-12); page 1, paragraphs 18,9; page 2, paragraphs 17,22; claims 1,6</td>
<td>1,4</td>
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Further documents are listed in the continuation of Box C

See patent family annex

* Special categories of cited documents

- 'A' document defining the general state of the art which is not considered to be of particular relevance
- 'B' earlier document but published on or after the international filing date
- 'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- 'O' document referring to an oral disclosure, use, exhibition or other means
- 'P' document published prior to the international filing date but later than the priority date claimed

**D. DATE OF ACTUAL COMPLETION OF THE INTERNATIONAL SEARCH**

14 February 2007

**E. DATE OF MAILING OF THE INTERNATIONAL SEARCH REPORT**

07/03/2007

Name and mailing address of the ISA/

European Patent Office, P B 5818 Patentlaan 2 NL-2280 HV RUSWIX

Tel (+31-70) 340-2040, Tx 31 651 epo nl, Fax (+31-70) 340-3016

Authorized officer

Collins, Sally

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**INTERNATIONAL SEARCH REPORT**

Information on patent family members

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