(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) **EP 1 909 840 B9**

(12) **CORRECTED EUROPEAN PATENT SPECIFICATION**

(15) Correction information:
Corrected version no 1 (W1 B1)
Corrections, see
Description Paragraph(s) 11-12, 15, 19

(48) Corrigendum issued on:
04.09.2013 Bulletin 2013/36

(45) Date of publication and mention of the grant of the patent:
20.02.2013 Bulletin 2013/08

(21) Application number: **06764238.9**

(22) Date of filing: **20.07.2006**

(51) Int Cl.:
A61K 8/02 *(2006.01)* ***A61K 8/97*** *(2006.01)*
A61K 9/06 *(2006.01)* ***A61K 9/70*** *(2006.01)*
A61K 47/10 *(2006.01)* ***A61L 15/44*** *(2006.01)*
A61L 26/00 *(2006.01)* ***A61K 9/00*** *(2006.01)*
A61K 31/185 *(2006.01)* ***A61K 31/23*** *(2006.01)*
A61K 47/32 *(2006.01)* ***A61K 8/49*** *(2006.01)*
A61K 36/23 *(2006.01)* ***A61L 15/40*** *(2006.01)*

(86) International application number:
PCT/EP2006/064461

(87) International publication number:
WO 2007/010023 (25.01.2007 Gazette 2007/04)

(54) **MEDICATED GAUZE**

ARZNEISTOFFE ENTHALTENDE GAZE

GAZE MEDICALE

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LI LT LU LV MC NL PL PT RO SE SI SK TR

(30) Priority: **21.07.2005 IT MI20051396**

(43) Date of publication of application:
16.04.2008 Bulletin 2008/16

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Description

FIELD OF THE INVENTION

[0001] The present invention relates to a medicated gauze for tissue repair of cutaneous lesions.

STATE OF THE ART:

[0002] The process of tissue repair of a cutaneous lesion, independently from the underlying cause, occurs by a sequence of events that is always identical and very complex, involving a high number of cells and chemical mediators.

[0003] This process is spontaneously activated following a cutaneous lesion.

[0004] Under certain conditions, however, the process of tissue repair is delayed, due to a persistent harmful stimulus and/or alterations of the biochemical and cellular balance, possibly leading to chronic cutaneous lesions.

[0005] For instance, these lesions are represented by ischemic, diabetic, venous ulcers and by decubitus lesions that do not reepithelize.

[0006] The treatment of chronic cutaneous lesions involves a triple therapeutic approach: general therapy, etiological therapy and local therapy. As far as local therapy is concerned, modern technology has set up a series of new concept medications, defined as "advanced", which unlike traditional medications, keep the wound in a moist microenvironment.

[0007] Among the latter type of medications, medicated gauzes turned out to be especially effective, and particularly the Fitostimoline gauze® containing a *Triticum vulgare* extract as active principle.

[0008] *Centella Asiatica* is a plant of Indian origin that is used, mostly as total triterpenic fraction, in many medicinal products for treatment of idiopathic or secondary chronic venous insufficiency and of varices complications, in delayed cicatrization and alterations of cutaneous trophism. The components of the total triterpenic fraction, which apparently accounts for the active fraction of *Centella,* are asiaticoside (40%), asiatic acid (30%) and madecassic acid (30%).

[0009] For instance, preparations for topical use, present on the market as powder or ointment, contain the total triterpenic fraction of *Centella Asiatica* in an amount of 2 gm or 1gm, respectively.

[0010] Widgerow et al. has already described that Centalla asiatica can be comprised in an ointment which is applied to the skin surface by using a microporous tape (Widgerow et al., New Innovations in Scar Mangagement, Aesth. Plast. Surg., 24: 227-234, 2000).

SUMMARY OF THE INVENTION:

[0011] The present inventors have now found that when a *Centella Asiatica* extract, containing not less than 4% of total triterpenic fraction, is used in association with allantoin and an Urtica dioica extract containing at least 0,3% by weight of total steroids, a synergistic effect is observed on the cicatrizant activity of both these active principles.

[0012] In fact, as illustrated in the following examples, gauzes impregnated with allantoin-containing ointment an Urtice dioica extract containing at least 0,3% by weight of total steroids and with very low doses of *Centella Asiatica* extract, that are much lower compared to those used in the above said medicinal products, show an efficacy in the treatment of cutaneous lesions that is tendentially superior to that of Fitostimoline gauzes®.

[0013] Therefore, the present invention relates to a sterile medicated gauze comprising as active principles allantoin, a *Centella Asiatica* extract and, an *Urtica dioica* extract in association with dermatologically compatible excipients, and relates also to a gauze, preferably made of hydrophilic cotton.

[0014] Moreover, the present invention relates to the use of a mixture comprising allantoin, a *Centella Asiatica* extract and an *Urtica dioica* extract for preparation of a medicament, in the form of medicated gauze, for topical treatment of all dermal tissue alterations involving reactivation of epithelial neoformation processes.

DETAILED DESCRIPTION OF THE INVENTION

[0015] A first object of the present invention is a medicated gauze comprising as active principles allantoin and an extract obtained from *Centella Asiatica* leaves, containing not less than 4% of total triterpenic fraction, estimated as asiaticoside, and an Urtica dioica extract containing at least 0,3% by weight of total steroids in association with dermatologically compatible excipients.

[0016] A preferred embodiment of the present invention involves, an extract from *Urtica dioica* containing least 0.4% of total sterols, estimated as β-sitosterol.

[0017] The above said extracts are preferably dry extracts.

[0018] Alternately, in presence of a dry extract from *Urtica dioica,* the above said ointment contains, by weight, from 0.05% to 0.2% of dry extract from *Centella Asiatica,* from 0.01% to 0.03% of dry extract from *Urtica dioica* and from 0.4% to 1.6% of allantoin.

[0019] Preferably, the sterile medicated gauze impregnated with the above said ointment is based on polyethylene glycols. In the ointment impregnating the medicated gauze of the present invention, particularly preferred is the use of a mixture of polyethylene glycols having a molecular weight of 400, 1500 and 4000 Da. Moreover, the ointment according to the present invention contains dermatologically compatible excipients, as for instance antioxidants, preservatives, emulsifiers and humidifiers.

[0020] A further object of the present invention is a medicated sterile gauze consisting of a gauze uniformly impregnated with the above said ointment.

[0021] Preferably, the gauze of the present invention is an hydrophilic cotton gauze. As an alternative to the gauze of the present invention, it is possible to use polyurethane supports with modulable porosity, made of polyvinyl alcohol or nonwoven tissue.

[0022] The medicated gauze of the present invention is impregnated with an amount of the above said ointment ranging from 0.03 to 0.05 gm per cm^2 and preferably equal to 0.04 gm per cm^2.

[0023] The gauze according to present invention is stored in an hermetically sealed aluminium bag in order to maintain sterility.

[0024] As shown in the following experimental examples, the medicated gauze, according to present invention, is especially effective in inducing reepithelization of cutaneous lesions. In fact, the combination of allantoin and *Centella Asiatica* extract produces a synergy suitable to support the reepithelization process, that is further stimulated if an *Urtica dioica* extract is also added.

[0025] Therefore, an object of the present invention is the use of a mixture of allantoin, *Centella Asiatica* extract and, *Urtica dioica* extract for the preparation of a medicament, preferably in the form of medicated gauze, for topical treatment of cutaneous lesions, particularly chronic cutaneous lesions. According to a particularly preferred embodiment, the medicated gauze of the present invention is especially effective on ulcero-dystrophic alterations (varicose ulcers, decubitus sores, torpid sores, fistula tracts, rhagades etc.); burns; lesions resulting from delayed post-operative cicatrization and abrasions.

[0026] Preferably, treatment of the above said lesions with the medicated gauze of the present invention requires at least one or two daily applications on the lesion.

[0027] The present invention will be now better illustrated by the following examples.

EXAMPLE 1

[0028] A medicated gauze was prepared by soaking a hydrophilic cotton gauze in 0.04gm/cm^2 ointment having the following percent composition

	Percentage by weight
D.E. *Centella Asiatica*	0.10%
D.E. *Urtica Dioica*	0.01%
Allantoin powder	0.80%
PEG 400	35%
PEG 1500	16%
PEG 4000	16%
Sorbitol	7.26%
Water	14.9%
Menthol	0.02%
Glycerol	4.5%
Vaseline	2.2%
Cetylic Alcohol	0.75%
Stearylic Alcohol	0.75%
O.e cinnamon	0.005%
Phenoxyethanol	1%
Tocopherol Acetate	0.50%

EXAMPLE 2

Clinical investigation

[0029] Evaluation of the efficacy of the products illustrated in example 1 was done on chronic cutaneous lesions.
[0030] The investigation was made on 40 patients (32 women with a mean age of 77 years and 8 men with a mean age of 76 years) with cutaneous lesions of size smaller than 20 cm^2, not infected and characterized by stage I or II depth.
[0031] The depth of cutaneous lesions has been classified as follows:

Stage I: superficial lesion, which does not cross the dermal layer of skin;
Stage II: medium lesion, affecting only the subcutaneous layer.

[0032] Patients have been divided into two homogeneous groups of 20 patients each, based on age, type, stage and surface of the lesion, as well as perilesional edge.
[0033] The first group of patients has been treated with the impregnated gauze of example 1, while the second group has been treated with Fitostimoline gauzes© (gauzes saturated with 4gm of cream containing in 100 gm: 15 gm aqueous extract from *Triticum vulgare,* with 200 mg/100 ml dry residue, and 1 gm 2-phenoxyethanol).
[0034] Table I shows the type of lesions in patients belonging to the two groups:

	Gauze example 1 group	**Fitostimoline gauze group**
Type of lesion	**Number of patients**	Number of patients
Venous ulcer	6	7
Vasculitic ulcer	4	2
Mixed ulcer	4	4
Post-traumatic ulcer	4	3
Post-surgical ulcer	1	0
Pressure ulcer	1	4

[0035] Before starting the treatment, all ulcers were subjected to normal cleansing; moreover, all patients started a specific medical therapy for the concomitant pathology.
[0036] All patients underwent two daily medications with the gauze of example 1 or with the Fitostimoline gauze for four weeks. Evaluation of the state of cutaneous lesion has been made at baseline, before treatment and in subsequent weekly controls, throughout the observation period, taking in consideration the following parameters during the control visits: area and diameters of the lesion in centimetres, aspect of background, margins and depth of the lesion.
[0037] For each lesion, the daily reepithelization index was calculated (IGR), expressing the daily percent reepithelization as cm^2 of the lesion.
[0038] This index is calculated according to the following formula:

$$IGR = \frac{Ext\ T_o - Ext\ T_x}{Ext\ T_o} \Big/ X$$

where

Ext T_o: extent of the lesion at the beginning of the treatment
Ext T_x: extent of the lesion after x days of treatment
X: days of treatment

[0039] A clinical judgement on the progress of the cicatrization process has been then assigned, based on the criteria summarized in table II:

Clinical judgement	IGR	% reepithelization at the end of treatment
Excellent	IGR ≥ 0.032	≥ 90% 90% of the lesion area
Good	0.018 ≤ IGR < 0.032	≥ 50% of the lesion area
Mediocre	0.004 s IGR < 0.018	≥ 10% of the lesion area
Unchanged	0.000 ≤ IGR < 0.004	< 10% of the lesion area
Worsened	IGR< 0	Increase of the lesion area compared to baseline
Not assessable	IGR not determined	Drop out

[0040] For a better evaluation of the results, the two study groups have been each divided into four subgroups, based on the extent of the lesion at the beginning of the treatment (Ext To in cm^2), as shown in the table III:

Gauze example 1 Group			Fitostimoline Group	
Subgroup	Patients No.	Range for Ext T_0	Patients No.	Subgroup
A1	9	1,00 ≤ Est T_0 < 5,000	10	F1
A2	5	5,00 ≤ Est T_0 < 10,00	5	F2
A3	4	10,00 ≤ Est T_0 < 15,00	3	F3
A4	2	15,00 ≤ Est T_0 < 20,00	2	F4

Comparison between the results obtained from the two study groups:

[0041] Table IV shows a comparison between clinical judgements obtained from the two study groups, for each subgroup:

Subgroup	Clinical judgement	Gauze Ex.1 Group	Fitostimoline gauze Group
A1-F1	Excellent	5	4
	Good	1	3
	Mediocre	2	2
	Unchanged	1	1
	Worsened	0	0
	Not assessable	0	0
A2-F2	Excellent	0	0
	Good	4	3
	Mediocre	1	2
	Unchanged	0	0
	Worsened	0	0
	Not assessable	0	0

A3-F3	Excellent	1	0
	Good	2	1
	Mediocre	1	2
	Unchanged	0	0
	Worsened	0	0
	Not assessable	0	0

(continued)

Subgroup	Clinical judgement	Gauze Ex.1 Group	Fitostimoline gauze Group
A4-F4	Excellent	0	0
	Good	1	1
	Mediocre	1	1
	Unchanged	0	0
	Worsened	0	0
	Not assessable	0	0

[0042] Table V shows a comparison between the global clinical judgement obtained from the two study groups:

Clinical judgement	Gauze example 1 Group	Fitostimoline Group
Excellent	6	4
Good	8	8
Mediocre	4	5
Unchanged	2	3
Worsened	0	0
Not assessable	0	0

Satisfactory results have been obtained in both study groups.

[0043] However, better results have been obtained with the gauze according to the present invention.
[0044] In particular, daily reepithelization index values were on average higher than those obtained with Fitostimoline gauzes, regardless of the extent and typology of the lesion.

Claims

1. A sterile medicated gauze for the reepithelization of cutaneous lesions impregnated with an ointment **characterised in that** it comprises as active principles a *Centella Asiatica* extract, containing not less than 4% by weight of total triterpenic fraction, an *Urtica dioica* extract containing at least 0.3% by weight of total sterols and allantoin, in association with dermatologically compatible excipients.

2. A sterile medicated gauze according to claim 1, **characterised by** the fact of comprising from 0.05% to 0.2% by weight of dry extract from Centella Asiatica, from 0.01% to 0.03% by weight of Urtica dioica and from 0.4% to 1.6% by weight of allantoin.

3. A sterile medicated gauze according to claim 1 wherein the *Urtica dioica* extract contains 0.4% by weight of total sterols.

4. A sterile medicated gauze according to claim 1 or 2, wherein said *Centella Asiatica* extract contains 4% by weight of total triterpenic fraction.

5. A sterile medicated gauze according to claims 1 to 4, containing in addition polyethylene glycols.

6. A sterile medicated gauze according to claim 5, wherein said polyethylene glycols are a mixture of polyethylene glycols having molecular weights of 400, 1500 and 4000 Da.

7. A sterile medicated gauze according to claim 1, wherein the support is a hydrophilic cotton gauze.

8. A sterile medicated gauze according to claim 1, wherein said gauze is impregnated with an amount of said ointment comprised between 0.03 and 0.05 gm per cm^2.

9. A sterile medicated gauze according to claim 8, wherein said gauze is impregnated with 0.04 gm per cm^2 of said ointment.

10. A sterile medicated gauze impregnated with an ointment comprising as active principles a Centella Asiatica extract, containing not less than 4% by weight of total triterpenic fraction, an Urtica dioica extract containing at least 0.3% by weight of total sterols and allantoin, in association with dermatologically compatible excipients for use in the re-epithelization of cutaneous lesions.

11. A sterile medicated gauze according to the use of claim 10, wherein said cutaneous lesions are chronic cutaneous lesions.

12. A sterile medicated gauze according to the use of claim 11, wherein said cutaneous lesions are ulcero-dystrophic alterations,varicose ulcers, decubitus sores, torpid sores, fistula tracts, rhagades, burns; lesions resulting from delayed post-operative cicatrization and abrasions.

Patentansprüche

1. Sterile arzneimittelhaltige Gaze zur Epithelneubildung bei Hautverletzungen, wobei diese Gaze mit einer Salbe getränkt ist, **dadurch gekennzeichnet, dass** diese Salbe als Wirkstoffe einen Auszug aus *centella asiatica,* welcher nicht mehr als 4 Gew.-% einer Triterpen-Fraktion enthält, und einen Auszug aus *urtica dioica,* welcher mindestens 0,3 Gew.-% an Gesamtsterolen und Allantoin enthält, zusammen mit dermatologisch verträglichen Trägerstoffen umfasst.

2. Sterile arzneimittelhaltige Gaze nach Anspruch 1, **gekennzeichnet durch** die Tatsache, dass sie trockene Auszüge von 0,05 bis 0,2 Gew.-% aus *centella asiatica,* von 0,01 bis 0,03 Gew.-% aus *urtica dioica* und von 0,4 bis 1,6 Gew.-% aus Allantoin umfasst

3. Sterile arzneimittelhaltige Gaze nach Anspruch 1, bei welcher der Auszug aus *urtica dioica* 0,4 Gew-% an Gesamtsterolen enthält.

4. Sterile arzneimittelhaltige Gaze nach Anspruch 1 oder 2, bei welcher der genannte Auszug aus *urtica dioica* 4 Gew.-% einer Gesamtfraktion aus Triterpen enthält.

5. Sterile arzneimittelhaltige Gaze nach Anspruch 1 bis 4, welche zusätzlich Polyethylenglykole enthält.

6. Sterile arzneimittelhaltige Gaze nach Anspruch 5, bei welcher die genannten Polyethylenglykole eine Mischung aus Polyethylenglykolen mit Molekulargewichten von 400, 1500 und 4000 Da sind.

7. Sterile arzneimittelhaltige Gaze nach Anspruch 1, bei welcher das Trägermaterial eine hydrophile Gaze aus Baumwolle ist.

8. Sterile arzneimittelhaltige Gaze nach Anspruch 1, bei welcher die genannte Gaze mit einer gewissen Menge an der genannten Salbe getränkt ist, welche zwischen 0,03 und 0,05 g/cm^2 liegt.

9. Sterile arzneimittelhaltige Gaze nach Anspruch 8, bei welcher die genannte Gaze mit einer Menge von 0,04 g/cm^2 der genannten Salbe getränkt ist.

10. Sterile arzneimittelhaltige Gaze, welche mit einer Salbe getränkt ist, welche als Wirkstoffe einen Auszug aus *centella asiatica,* welcher nicht mehr als 4 Gew.-% einer Triterpen-Fraktion enthält, und einen Auszug aus *urtica dioica,* welcher mindestens 0,3 Gew.-% an Gesamtsterolen und Allantoin enthält, zusammen mit dermatologisch verträglichen Trägerstoffen umfasst, zur Anwendung bei der Epithelneubildung bei Hautverletzungen.

11. Sterile arzneimittelhaltige Gaze gemäß der Anwendung nach Anspruch 10, bei welcher die genannten Hautverletzungen chronische Hautverletzungen sind.

12. Sterile arzneimittelhaltige Gaze gemäß der Anwendung nach Anspruch 11, bei welcher es sich bei den genannten Hautverletzungen um ulcerodystrophe Veränderungen, ulcus varicosum, entzündlichem Dekubitalulkus, torpiden Geschwüren, Fistelkanälen, Fissuren, Brandwunden sowie um Verletzungen handelt, die sich aus späteren post-operativen Vernarbungen und Abrasionen ergeben.

Revendications

1. Gaze médicale stérile pour la reépithélialisation de lésions cutanées imprégnée d'un onguent, **caractérisée en ce qu'**elle comprend comme principes actifs un extrait de *Centella Asiatica,* contenant pas moins que 4% en poids de la fraction tripterpénique totale, un extrait de *Urtica dioica* contenant au moins 0,3% en poids de stérols totaux et de l'allantoine, en association avec des excipients dermatologiquement compatibles.

2. Gaze médicale stérile selon la revendication 1, **caractérisée par le fait qu'**elle comprend de 0,05% à 0,2% en poids d'un extrait sec de Centella Asiatica, de 0,01% à 0,03% en poids de Urtica dioica et de 0,4% à 1,6% en poids d'allantoine.

3. Gaze médicale stérile selon la revendication 1, où l'extrait de Urtica dioica contient 0,4% en poids de stérols totaux.

4. Gaze médicale stérile selon la revendication 1 ou 2, où ledit extrait de Centella Asiatica contient 4% en poids de la fraction triterpénique totale.

5. Gaze médicale stérile selon les revendications 1 à 4, contenant en plus des glycols de polyéthylène.

6. Gaze médicale stérile selon la revendication 5, où lesdits glycols de polyéthylène sont un mélange de glycols de polyéthylène ayant des poids moléculaires de 400, 1500 et 4000 Da.

7. Gaze médicale stérile selon la revendication 1, où le support est une gaze en coton hydrophile.

8. Gaze médicale stérile selon la revendication 1, où ladite gaze est imprégnée d'une quantité dudit onguent comprise entre 0,03 et 0,05 gm par cm^2.

9. Gaze médicale stérile selon la revendication 8, où ladite gaze est imprégnée de 0,04 gm par cm^2 dudit onguent.

10. Gaze médicale stérile imprégnée d'un onguent comprenant comme principes actifs un extrait de Centella Asiatica, contenant pas moins que 4% en poids de la fraction triterpénique totale, un extrait de Urtica dioica contenant au moins 0,3% en poids de stérols totaux et de l'allantoine, en association avec des excipients dermatologiquement compatibles pour l'utilisation dans la re-épithélialisation de lésions cutanées.

11. Gaze médicale stérile selon l'utilisation de la revendication 10, où lesdites lésions cutanées sont des lésions cutanées chroniques.

12. Gaze médicale stérile selon l'utilisation de la revendication 11, où lesdites lésions cutanées sont des altérations ulcéro-dystrophiques, ulcères variqueux, plaies de décubitus, plaies torpides, étendues de fistules, crevasses, brûlures; des lésions résultant d'une cicatrisation post-opératoire retardée et d'abrasions.

REFERENCES CITED IN THE DESCRIPTION

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Non-patent literature cited in the description

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