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(54) Title: COMPOSITION OF FILM-FORMING SOLUTION TYPE, COMPRISING VITAMIN D OR A DERIVATIVE THEREOF AND A CORTICOSTEROID, AND USE THEREOF IN DERMATOLOGY

(57) Abstract: The present invention relates to a composition comprising two solubilized active agents, vitamin D or a derivative thereof and a corticosteroid, said composition being a film-forming solution, and also to the use thereof in dermatology.

Composition of film-forming solution type, comprising vitamin D or a derivative thereof and a corticosteroid, and use thereof in dermatology

The invention relates to a novel composition of film-forming solution type, intended for application to the nails, comprising two solubilized active agents which are:

- vitamin D or a derivative thereof, preferably calcitriol,
- and a corticosteroid, preferably clobetasol 17-propionate,

and also to the use thereof in dermatology in the treatment of nail psoriasis.

Psoriasis is a chronic inflammatory disease of the skin which affects approximately 5% of the French population. This disease manifests itself through lesions, giving rise to quite distinct forms of psoriasis.

Among the latter, nail psoriasis involves approximately half the individuals suffering from the disease. The nails of the hands are affected more than those of the feet. The nail, which grows in an accelerated manner, is then subjected to certain alterations - due to keratinization problems - depending on the location of the psoriasis. It sometimes exhibits at its surface small depressions which give it a thimble-like appearance. Sometimes, salmon-coloured marks appear, or even a discoloration. The nail can also undergo thickening which can detach it from its bed. Finally, it sometimes exhibits transverse or longitudinal striations. The inflammation can also extend under the nail: in this case, the lesions are not in contact with the air and heal with difficulty.

This pathology in the nail is generally difficult to treat, even more so since few treatments are available.

Among the current treatments proposed for topical administration, mention may, by way of example, be made of:

- calcipotriol solution;
- cyclosporin or anthralin ointment ("*Treatment of psoriatic nails with topical cyclosporin: a prospective, randomized placebo-controlled study*" Cannavo et al., Dermatology 2003; 206 (2): 153-6);
- the application of a class I corticosteroid;
- 5-fluorouracil cream.

Antifungal treatments can also be prescribed in the case of secondary infection.

None of these treatments is very effective. Thus, other routes and combinations have been researched, for instance:

- tazarotene gel ("*Tazarotene 0.1% gel in the treatment of fingernail psoriasis: a double-blind, randomized, vehicle-controlled study*" Scher RK et al., Cutis 2001 Nov.; 68 (5) 355-8 and "*Tazarotene 0.1% gel for psoriasis of the fingernails and toenails: an open, prospective study*" Bianchi L et al., Br J Dermatol. 2003 Jul.; 149 (1): 207-9);
- the combination of cyclosporin administered orally with a calcipotriol cream ("*Nail psoriasis: combined therapy with systemic cyclosporin and topical calcipotriol*" Feliciani et al., J Cutaneous Medicine Surgery: Incorporating Medical and Surgical Dermatology 2004; 8 (2): 122-5);
- combination, by topical administration, of a calcitriol cream and a clobetasol 17-propionate cream ("*Nail psoriasis: a combined treatment using calcipotriol cream and clobetasol propionate cream*" Rigopoulos et al., Acta Derm Venereol. 2002; 82 (2): 140).

However, the combination of active ingredients is not used conventionally in the treatment of dermatological conditions. The difficulties mainly encountered by those skilled in the art when combining two active ingredients are the problems of chemical instability and interactions that the active ingredients may exhibit when they are present in the same formulation.

Vitamin D and derivatives thereof are unstable in aqueous media, and sensitive to acidic pHs, whereas corticosteroids, and more particularly clobetasol 17-propionate, are themselves sensitive to basic media.

The applicant has described, in application FR 2 848 454, a combination of calcitriol with a corticosteroid in the treatment of certain dermatological conditions, without however proposing any stable pharmaceutical compositions combining the two active agents.

Moreover, in the field of dermatology and of the formulation of pharmaceutical compositions, those skilled in the art are led to search for compositions which not only must be physically and chemically stable, but also must make it possible to release the active agent and to promote the penetration thereof over the target zone in order to improve its effectiveness.

There existed therefore a need for a specific composition for the nails, comprising vitamin D or a derivative thereof and a corticosteroid, said composition being stable and well tolerated.

The present invention consists in providing a novel formulation, of film-forming solution type, comprising vitamin D or a derivative thereof, preferably calcitriol, combined with a corticosteroid, preferably clobetasol 17-propionate. This composition is of use in

the treatment of nail psoriasis. The solution form allows local application of the treatment without systemic exposure; it is therefore well tolerated. Furthermore, by virtue of its composition, this solution allows a gradual release of the active ingredients.

The present invention therefore relates to a composition comprising, in a physiologically acceptable medium, as pharmaceutical active agents, vitamin D or a derivative thereof and a corticosteroid, characterized in that said composition is a film-forming solution. This solution is preferably a nail varnish.

The present invention preferably relates to a composition comprising, in a physiologically acceptable medium, as pharmaceutical active agents, calcitriol and clobetasol 17-propionate, characterized in that said composition is a film-forming solution, preferably a nail varnish.

In the text which follows, clobetasol 17-propionate will be referred to as clobetasol propionate.

The term "physiologically acceptable medium" is intended to mean any medium that is compatible with the skin, the mucous membranes and the integuments.

The term "film-forming solution" is intended to mean a solution containing at least one film-forming polymer. Such a solution is preferably intended for application to the nails.

Preferably, the film-forming solution according to the invention is a nail varnish.

Advantageously, the film-forming solution according to the invention is a nonaqueous solution. The term "nonaqueous solution" is intended to mean a solution

free of added water. The solution may, however, contain an amount of residual water not exceeding 5% of the total concentration of solvents/cosolvents of the composition. Preferably, the film-forming solution according to the invention is a nonaqueous nail varnish.

Such a composition is therefore for topical use.

Such compositions can also be sprayed with or without propellant gas.

When the composition contains a propellant gas, it is chosen from the group consisting of propane, butane, isobutane, dichlorodifluoromethane, dichlorotetrafluoroethane, octafluorocyclobutane, nitrogen, CO_2 and dimethyl ether, or mixtures thereof.

According to a preferred form of the invention, the propellant gas is in liquefied form and its concentration is between 5% and 30% of the total composition.

According to a preferred embodiment of the invention, the composition is a film-forming solution, preferably a nail varnish, which comprises, in a physiologically acceptable medium, as pharmaceutical active agents, vitamin D or a derivative thereof and a corticosteroid, which are present in solubilized form.

The term "solubilized form" is intended to mean a dispersion in the molecular state in a liquid, no crystallization of the active agents being visible to the naked eye nor even under a cross-polarized optical microscope.

In the subsequent text, the amounts are expressed as percentage by weight relative to the total weight of the composition (m/m).

In one embodiment of the invention, the film-forming solutions as defined above comprise:

a) vitamin D or a derivative thereof and a corticosteroid, which are solubilized,

b) an organic solvent/cosolvent mixture,

c) and at least one film-forming agent.

In a preferred embodiment of the invention, the film-forming solutions as defined above comprise:

a) calcitriol and clobetasol propionate, which are solubilized,

b) an organic solvent/cosolvent mixture,

c) and at least one film-forming agent.

The term "vitamin D" is intended to mean the various forms of vitamin D, such as, for example, vitamin D_1, D_2, D_3 or vitamin D_4.

The term "vitamin D derivatives" is intended to mean compounds which exhibit biological properties similar to those of vitamin D, in particular vitamin D response element (VDRE) transactivating properties, such as an agonist or antagonist activity with respect to vitamin D receptors. These compounds are not generally natural metabolites of vitamin D, but are in particular synthetic compounds comprising the vitamin D backbone with modifications on the side chains and/or comprising modifications in the backbone itself.

Among vitamin D derivatives, mention may, by way of nonlimiting example, be made of calcipotriol, 25-hydroxyvitamin D_3, 1α-hydroxyvitamin D_3, calcitriol or 1α,25-dihydroxyvitamin D_3, 1α,25,26-trihydroxyvitamin D3, 1α,23,25-trihydroxyvitamin D3, 24,25-dihydroxyvitamin D3, 1α,25-dihydroxyvitamin D2, 1α-hydroxyvitamin D2, 1α,24-dihydroxyvitamin D2 and 1α,24-dihydroxyvitamin D3 (or tacalcitol), and mixtures thereof.

According to a preferred embodiment of the invention, the vitamin D derivative is calcitriol.

The amount of vitamin D or derivatives thereof that can be used according to the invention is between 0.00001% and 0.1% m/m, preferably between 0.0001% and 0.001% m/m, and preferably between 0.0002% and 0.0005% m/m. This amount is preferably equal to 0.0003% m/m.

Among corticosteroids, mention may, by way of non-limiting example, be made of clobetasone and esters thereof such as the 17-butyrate, clobetasol and esters thereof such as the 17-propionate, hydrocortisone and esters thereof such as the 17-butyrate, cortisone and esters thereof such as the 21-acetate, prednisolone and esters thereof such as pivalate, miconazole, prednisone, triamcinolone and esters and ethers thereof such as triamcinolone acetonide, methylprednisolone, fluometholone, fluocinolone and esters and ethers thereof such as fluocinolone acetonide, desonite, beta-methasone and esters thereof such as the 21-acetate, the 17-adamantoate, the 17-benzoate, the 17-valerate and the 17,21-dipropionate, and dexamethasone, and mixtures and derivatives thereof.

The term "corticosteroid derivatives" is intended in particular to mean their pharmaceutically acceptable salts with a base, such as the disodium phosphate salts.

In a particular embodiment of the invention, the corticosteroid is a clobetasol ester such as clobetasol 17-propionate, called clobetasol propionate in the present application.

The amount of corticosteroid that can be used according to the invention is between 0.0001% and 0.1% m/m,

preferably between 0.001% and 0.05% m/m, and preferably between 0.0002% and 0.0005% m/m. This amount is preferably equal to 0.025% m/m.

According to a preferred embodiment of the invention, the composition is a film-forming solution, preferably a nail varnish, which also contains at least one promoter of absorption into the nail. Preferably, the composition contains two absorption promoters.

The expression "promoter of absorption into the nail" is intended to mean pharmaceutically acceptable chemical compounds capable of increasing the permeability of the nail with respect to the active ingredients, so as to increase the kinetics of penetration of these active ingredients through the nail.

The absorption promoters that can be used according to the invention are urea, glycols, such as propylene glycol, butylene glycol, hexylene glycol, ethylene glycol or polyethylene glycols, glycol monoethers, such as the ethylene glycol monoethers sold under the names "Dowanol PM, DPM, TPM, PnB, PPH, DPnB, TPnB, PMA", glycol polyethers such as ethoxydiglycol, propylene glycol dimethyl ether or dipropylene glycol dimethyl ether, dimethyl sulphoxide, amino acids and derivatives thereof such as N-acetyl-L-cysteine, and a mono- or polycarboxylated C_1 to C_{18}, preferably C_1 to C_{12}, carboxylic acid and derivatives thereof such as hydroxymonocarboxylic acids, hydroxydicarboxylic acids, or the free acids, and also the lactones, the salts, the esters derived therefrom, caprolactam, dimethyl-acetamide and dimethylisosorbide. Other absorption promoters that can be used according to the invention are also mentioned in US patent 6 455 592.

Among the C_1 to C_{12} aliphatic carboxylic acids, and in particular hydroxyl acids, mention may, for example, be

made, without implied limitation, of methanoic acid, 2-methylbutanoic acid, propanoic acid, 2-methyl-propanoic acid, 2,2-dimethylpropanoic acid, decanoic acid, octanoic acid, hex-2-enoic acid, heptanoic acid, 6-methylheptanoic acid, 3-ethylpentanoic acid, 3-chloropentanoic acid, 2-hydroxypropanoic acid, 2-chloro-4-hydroxyhexanoic acid, hexanedioic acid, octadecanoic acid, 4-oxopentanoic acid, 6-hydroxy-4-oxonanoic acid, 2-ketopropanoic acid, tartronic acid, malic acid, tartaric acid, glucaric acid, citric acid, lactic acid, glycolic acid, isocitric acid, tropic acid, 5-hydroxylauric acid and 3-hydroxy-4-methoxy-mandelic acid, or mixtures thereof.

In particular, the solution according to the invention may comprise, as aliphatic carboxylic acid, lactic acid or citric acid, preferably lactic acid.

Preferably, the absorption promoters are the pairs urea/lactic acid or urea/N-acetyl-L-cysteine.

The urea is used at a concentration of less than 15% by weight of urea relative to the weight of the non-volatile part of the composition, in particular at a concentration of less than 14% by weight of urea relative to the weight of the non-volatile part of the composition, preferably between 7% and 14%, and more particularly between 9% and 13% by weight of urea relative to the weight of the non-volatile part of the composition; the lactic acid is used in an amount of between 0.01% and 15% m/m, and preferably between 1% and 10%, in particular between 1% and 7%; and the N-acetyl-L-cysteine is used in an amount of between 0.5% and 10% m/m, preferably between 1% and 7% m/m.

The weight proportion of ethoxydiglycol relative to the total weight of the composition is between 0.01% and 20% m/m, and preferably between 1% and 10%.

As mentioned above, the solution according to the invention contains a solvent.

The solvents and cosolvents can be chosen from the organic solvent family, and are class 3 solvents with a low toxic potential according to the ICH standards (Impurities: Guideline for Residual Solvents, International Conference of Harmonization), such as ethanol, isopropyl alcohol, acetone, methyl acetate, ethyl acetate, butyl acetate, alkyl methyl sulphoxides, such as dimethyl sulphoxide, 2-propanol, methyl isobutyl ketone, 1-butanol, dichloromethane or N-methyl-2-pyrrolidone, or mixtures thereof.

Among the solvents/cosolvents as described above, use will preferably be made of volatile organic solvents/ cosolvents, and more preferably a mixture consisting of ethanol and of at least one cosolvent chosen from ethyl acetate and butyl acetate.

The solvents/cosolvents can be used at the preferential concentrations ranging, respectively, from 10% to 90% and from 0% to 30% m/m, and more preferably ranging respectively from 10% to 80% and from 1% to 30% m/m.

Preferably, the vitamin D or derivatives thereof, preferably calcitriol, and the corticosteroid, preferably clobetasol propionate, are solubilized in the preferred solvent, i.e. ethanol.

Since the preparation of the compositions according to the invention requires the presence of at least one film-forming agent, the latter is preferably water-insoluble and chosen from:

- copolymers of monoalkyl esters of polyvinyl methyl ether and maleic acid, such as the butyl ester of polyvinyl methyl ether and maleic acid copolymer (butyl ester of PVM/MA copolymer) sold under the name Gantrez ES 425 by the company ISP,

- copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups derived from acrylic acid, such as the acrylate and ammonium methacrylate copolymer (acrylate/ ammonium methacrylate copolymer) sold under the name Eudragit RL 100 by the company Röhm Pharma,
- cellulose derivatives, such as the nitrocellulose or the ethylcellulose sold by the company Aqualon,
- polyurethane derivatives, such as the Avalures sold by the company Noveon.

Also useable as film-forming agent according to the present invention are polyvinylpyrrolidones and derivatives, such as poly-1-vinyl-2-pyrrolidone, polyvinylpyrrolidone/vinyl acetate copolymer and vinyl-pyrrolidone/dimethylaminoethyl methacrylate copolymer, the copolymer derived from vinylpyrrolidone/acrylic acid and lauryl methacrylate, polysaccharides such as, in particular, chitosans and derivatives, gums such as guar gum, carrageenan gums, karaya gum or xanthan gum, polyvinyl alcohols, polyacrylamides, acrylic/ methacrylic, polymethacrylate/butyl acrylate or acrylic/acrylate copolymers, cyanoacrylic polymers, or polyvinyl methyl ether/maleic anhydride copolymer.

The film-forming agent as described above is used at the preferential concentrations ranging from 0.01% to 50% m/m, preferably 5% to 30% m/m.

The composition can also contain a plasticizer. The plasticizer is preferably used at concentrations ranging from 0.001% to 10.00% m/m, preferably from 0.5% to 5% m/m. Among plasticizers, use is made, without this list being limiting, of compounds such as phthalates, triacetates or citrates, or mixtures thereof. The plasticizer is preferably triacetin.

The film-forming solution according to the invention can also comprise any additive normally used in the

cosmetics or pharmaceutical field, such as sequestering agents, wetting agents, adhesion agents, spreading agents, antioxidants, sunscreens, preserving agents, fillers, electrolytes, humectants, pigments, dyes, of usual bases or acids, which may be inorganic or organic, essential oils, cosmetic active agents, moisturizers, vitamins, essential fatty acids, or sphingolipids. Of course, those skilled in the art will take care to choose this or these optional additional compound(s) and/or the amount thereof, in such a way that the advantageous properties of the composition according to the invention are not, or are not substantially, impaired.

The invention also relates to the composition as described above, as a medicament.

Finally, the invention relates to the use of a composition as defined above, in the manufacture of a medicament for use in the prevention or treatment of nail psoriasis.

The invention will now be illustrated by means of the following nonlimiting examples.

Example 1: Composition

Starting materials	Amounts as % m/m
Clobetasol propionate	0.025
Calcitriol	0.0003
Lactic acid	4.00
Urea	2.50
Gantrez ES-435	20.00
Ethyl acetate	17.00
Butyl acetate	6.00
Ethanol	qs 100

Example 2: Composition

Starting materials	Amounts as % m/m
Clobetasol propionate	0.025
Calcitriol	0.0003
Urea	2.50
N-acetyl-L-cysteine	1.50
Eudragit RL100	14.00
Triacetin	1.50
Ethyl acetate	17.00
Butyl acetate	6.00
Ethanol	qs 100

Example 3: Composition

Starting materials	Amounts as % m/m
Clobetasol propionate	0.025
Calcipotriol	0.0003
Lactic acid	4.00
Urea	2.50
Gantrez ES-435	20.00
Ethyl acetate	17.00
Butyl acetate	6.00
Ethanol	qs 100

Example 4: Composition

Starting materials	Amounts as % m/m
Clobetasol propionate	0.025
Calcitriol	0.0003
Urea	2.50
N-acetyl-L-cysteine	1.50
Poly-1-vinyl-2-pyrrolidone	2.00
Ethyl acetate	17.00
Butyl acetate	6.00
Ethanol	qs 100

CLAIMS

1. Composition comprising, in a physiologically acceptable medium, as pharmaceutical active agents, vitamin D or a derivative thereof and a corticosteroid, characterized in that said composition is a film-forming solution.

2. Composition according to Claim 1, characterized in that the solution is a nail varnish.

3. Composition according to Claim 1 or 2, characterized in that the solution is a nonaqueous nail varnish.

4. Composition according to one of Claims 1 to 3, characterized in that the vitamin D or a derivative thereof is chosen from vitamin D_1, D_2, D_3 or D_4, calcipotriol, 25-hydroxyvitamin D_3, 1α-hydroxyvitamin D_3, calcitriol, 1α,25,26-trihydroxyvitamin D3, 1α,23,25-trihydroxyvitamin D3, 24,25-dihydroxyvitamin D3, 1α,25-dihydroxyvitamin D2, 1α-hydroxyvitamin D2, 1α,24-dihydroxyvitamin D2 and 1α,24-dihydroxyvitamin D3, and mixtures thereof.

5. Composition according to Claim 4, characterized in that the vitamin D derivative is calcitriol.

6. Composition according to one of Claims 1 to 5, characterized in that the corticosteroid is chosen from clobetasone, clobetasone 17-butyrate, clobetasol, clobetasol 17-propionate, hydrocortisone, hydrocortisone 17-butyrate, cortisone, cortisone 21-acetate, prednisolone, prednisolone pivalate, miconazole, prednisone, triamcinolone, triamcinolone acetonide, methylprednisolone, fluometholone, fluocinolone, fluocinolone acetonide, desonide, betamethasone, betamethasone 21-acetate, betamethasone 17-adamantoate, betamethasone 17-benzoate,

betamethasone 17-valerate, betamethasone 17,21-di-propionate and dexamethasone, and mixtures and derivatives thereof.

7. Composition according to Claim 6, characterized in that the corticosteroid is clobetasol propionate.

8. Composition according to one of Claims 1 to 7, characterized in that the active agents are present in solubilized form.

9. Composition according to one of Claims 1 to 8, characterized in that it comprises at least one absorption promoter chosen from the group consisting of urea, ethoxydiglycol, lactic acid and N-acetyl-L-cysteine.

10. Composition according to Claim 9, characterized in that it comprises two absorption promoters chosen from the pairs urea/lactic acid and urea/N-acetyl-L-cysteine.

11. Composition according to any one of Claims 1 to 10, characterized in that it comprises between 0.00001% and 0.1% of vitamin D or derivatives thereof by weight relative to the total weight of the composition, preferably between 0.0001% and 0.001% by weight, and more preferably between 0.0002% and 0.0005% by weight.

12. Composition according to any one of Claims 1 to 11, characterized in that it comprises 0.0003% of vitamin D or derivatives thereof by weight relative to the total weight of the composition.

13. Composition according to any one of Claims 1 to 12, characterized in that it comprises between 0.0001% and 0.1% of corticosteroid by weight relative to the total weight of the composition, preferably

between 0.001% and 0.05% by weight.

14. Composition according to any one of Claims 1 to 13, characterized in that it comprises 0.025% of corticosteroid by weight relative to the total weight of the composition.

15. Composition according to any one of Claims 1 to 14, characterized in that it comprises at least one film-forming agent chosen from poly-1-vinyl-2-pyrrolidone, butyl ester of polyvinyl methyl ether and maleic acid copolymer, and acrylate and ammonium methacrylate copolymer.

16. Composition according to any one of Claims 1 to 15, characterized in that it comprises ethanol and at least one cosolvent, said cosolvent being chosen from ethyl acetate and butyl acetate.

17. Composition according to Claim 16, characterized in that the vitamin D or derivatives thereof is solubilized in ethanol.

18. Composition according to Claim 16, characterized in that the corticosteroid is solubilized in ethanol.

19. Composition according to one of Claims 1 to 18, as a medicament.

20. Use of a composition according to any one of Claims 1 to 18, in the manufacture of a medicament for use in the prevention or treatment of nail psoriasis.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/004315

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K8/67 A61K8/63 A61Q3/02 A61K31/59 A61P17/06

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2001/006625 A1 (BOHN ET AL.) 5 July 2001 (2001-07-05) claims 1,2,4,5,8,12,16-19,21,22,24 paragraphs [0007], [0013], [0015] - [0017], [0022], [0023], [0025] examples 1-3	1-20
Y	WO 96/14048 A (SEIDENSCHNUR) 17 May 1996 (1996-05-17) claims 1,2,6,9,10 page 1, line 11 - line 15 page 3, line 5 - line 6 page 5, line 12 - line 19 page 6, line 18 - line 37 page 7, line 7 - line 11 example 1	1-20

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
17 August 2006	24/08/2006

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INTERNATIONAL SEARCH REPORT

International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	FR 2 848 454 A (GALDERMA RESEARCH & DEVELOPMENT) 18 June 2004 (2004-06-18) cited in the application claims 1-9,11 page 2, line 9 - line 12 page 2, line 28 - line 31 page 3, line 1 - line 30 page 4, line 12 - line 20	1-20
Y	US 4 871 723 A (MAKINO ET AL.) 3 October 1989 (1989-10-03) claim 1 column 5, line 6 - line 16	9
Y	US 5 565 462 A (EITAN ET AL.) 15 October 1996 (1996-10-15) column 3, line 4 - line 38	9,10
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