(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
1 June 2017 (01.06.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/091168 A1

(51) International Patent Classification:
A61K 9/00 (2006.01) *A61K 31/573* (2006.01)
A61K 9/12 (2006.01) *A61P 17/00* (2006.01)
A61K 31/4174 (2006.01) *A61P 31/10* (2006.01)

(21) International Application Number:
PCT/TR2015/050208

(22) International Filing Date:
28 November 2015 (28.11.2015)

(25) Filing Language: English

(26) Publication Language: English

(71) Applicant: **PHARMACTİVE İLAÇ SAN. VE TİC. A.Ş.** [—/TR]; Mahmutbey Mah. Dilmenler Cad., Aslanoba Plaza No:19 K:3, Bağcilar/İstanbul (TR).

(72) Inventors: **YILDIRIM, Ersin**; Pharmactive İlaç Fabrikasi, Atatürk Mah. Fatih Blv. No:32 ÇOSB, Çerkezköy/Tekirdağ (TR). **SOLMAZ, Mustafa Serkan**; Pharmactive İlaç Fabrikasi, Atatürk Mah. Fatih Blv. No:32 ÇOSB, Çerkezköy/Tekirdağ (TR). **BEYOĞLU, Suna**; Pharmactive İlaç Fabrikasi, Atatürk Mah. Fatih Blv. No:32 ÇOSB, Çerkezköy/Tekirdağ (TR). **GÜRPINAR, Hakan**; Pharmactive İlaç Fabrikasi, Atatürk Mah. Fatih Blv. No:32 ÇOSB, Çerkezköy/Tekirdağ (TR). **AKSU, Derya**; Pharmactive İlaç Fabrikasi, Atatürk Mah. Fatih Blv. No:32 ÇOSB, Çerkezköy/Tekirdağ (TR). **KARASU, Tolga Ramazan**; Pharmactive İlaç Fabrikasi, Atatürk Mah. Fatih Blv. No:32 ÇOSB, Çerkezköy/Tekirdağ (TR). **YILMAZ, Koray**; Pharmactive İlaç Fabrikasi, Atatürk Mah. Fatih Blv. No:32 ÇOSB, Çerkezköy/Tekirdağ (TR).

(74) Agent: **BULUT, Pinar**; FarmaPatent Limited Şirketi, GMK Bulvarı Leventler Apt. 42/5, Maltepe, 06440 Çankaya/Ankara (TR).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

WO 2017/091168 A1

(54) Title: A TOPICAL SPRAY COMPRISING ISOCONAZOLE NITRATE AND DIFLUOCORTOLONE VALERATE

(57) Abstract: The present invention relates to the topical spray compositions comprising difluocortolone valerate and isoconazole nitrate that are useful for treating inflammatory skin conditions accompanied by fungal infections.

A TOPICAL SPRAY COMPRISING ISOCONAZOLE NITRATE AND DIFLUOCORTOLONE VALERATE

Field of Invention

The present invention relates to the preperation of novel topical pharmaceutical compositions comprising a glucocorticoid derivative, such as difluocortolone and an antifungal derivative, such as isoconazole that are useful for treating inflammatory skin conditions accompanied by fungal infections.

Background of Invention

Topical preparations have been used for treating many diseases in many years. Combinations can be used for topical preparations. Combination formulations can include many kind of active ingredients such as member of corticosteroid, antifungal, vitamin, antibiotic, NSAID, antiseptic, antihistaminic etc. groups.

Topical preparations offers many potential advantages over conventional methods of drug administration. Topical formulations are applied directly to the skin. Advantages of using topical preparation arei) increased dose of medication where it is needed, ii) reduced side effects and toxicity to other organs.

Corticosteroids are group of natural and synthetic analogues of the hormones secreted by the hypothalamic-anterior pituitary-adrenocortical (HPA) axis, more commonly referred to as the pituitary gland. Corticosteroids are extremely potent anti-inflammatory agents with widespread application in both veterinary and human medicine. Corticosteroid medicines are mainly used for their effect in controlling inflammation, and topical corticosteroids are applied to the skin for the localised treatment of various inflammatory skin disorders.

Strong anti-inflammatory potency has been achieved with the corticosteroids as their water soluble and insoluble derivatives and these are also widely prescribed.

Difluocortolone is a member of corticosteroid drugs. It is a topical glucocorticoid used in various dermatoses. It is absorbed through the skin, bound to plasma albumin, and may cause adrenal suppression. It also can be administered as the valerate.

Diflucortolone can be used for all skin diseases which respond to topical corticoid therapy: contact dermatitis, contact eczema, occupational eczema vulgar, nummular, degenerative and seborrhoeic eczema, dyshidrotic eczema, eczema in varicose syndrome, anal eczema, eczema in children, neurodermatitis (endogenous eczema, atopic dermatitis), psoriasis, lichen ruber planus et verrucosus, lupus erythematosus discoides, first degree burns, sunburn, insect bites.

Difluocortolone valerate, chemical name is (6α,11β,16α)-6,9-Difluoro-11-hydroxy-16-methyl-3,20-dioxopregna-1,4-dien-21-yl valerate. The compound having the figure 1 is known as difluocortolone valerate.

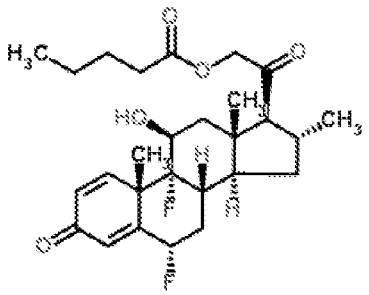

Figure 1

Diflucortolone is available as a cream, oily cream or ointment. The cream is most suitable for weepy areas of skin, as it is less greasier than the other two formulations and allows secretions from the skin to drain away. It is also more suitable for moist or hairy areas of skin. The oily cream is slightly more greasier and is suitable for skin that is neither weeping nor very dry. The ointment is more greasier again, and is suitable for very dry skin conditions. It provides a layer of oil on the surface of the skin that helps to prevent water from evaporating, thereby reducing dryness and scaling.

Many types of fungal germs (fungi) live harmlessly in the soil, on food, on our skin and in other places in the environment. However, some types of fungi can thrive and multiply on the surface of the body, to cause infection of the skin, nails, mouth or vagina.

Fungal infections of the skin, nails, vagina and mouth are quite common. They are rarely serious and don't usually spread deeper into the body. If you are otherwise healthy and have a normal immune system, it is rare for fungi to affect internal organs. However, fungal infections of the heart, lung, brain and other organs sometimes do occur. These internal fungal infections can be serious and, sometimes, life-threatening.

There are several different antifungal preparations that are used to treat various fungal infections. They come as creams, sprays, solutions, shampoos, tablets designed to go into the vagina (pessaries), medicines to take by mouth, and injections.

Isoconazole is an azole antifungal agent in the treatment of infections. It can be used pharmaceutically as an antifungal agent and an also antibacterial drug.Isoconazole destroys fungi by suppressing their ability to grow or reproduce.

Isoconazole nitrate, chemical name is 1-{2-[(2,6-Dichlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl}-1H-imidazole nitrate (1:1). The compound having the figure 2 is known as isoconazole nitrate.

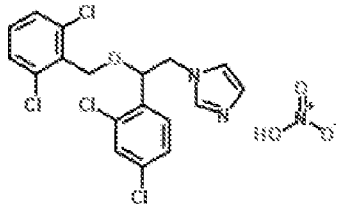

Figure 2

WO 2014/134394 relates to enhancing bioavailability of corticosteroid from oil-in-water emulsion, comprises varying the concentrations of surfactant i.e. ceteth-20, co-surfactants, emollients e.g. safflower oil, and water, for treating skin disorder e.g. dermatosis.

EP 1390031 discloses to a topical pharmaceutical composition comprising an antifungal and a second drug, for treating dermatophytes.

WO 2009/059191 describes to a composition, comprises antibacterial, antiinflammatory and antiseptic agent, useful e.g. to treat furunculosis, otomycosis, herpes oticus, dermatoses, perichondritis, chronic otitis media, vestibular neruonitis and chronic otitis externa.

EP 1776109 relates to a pharmaceutical composition comprises orbifloxacin or one of its salts, antifungal amount of triazole compound, and corticosteroid, for treatment of otic infection in animal.

There are already existing drugs comprising isoconazole nitrate in the form of topical sprays as named Travogen, Icaden, Icaden VSFF marketed by Bayer AG.There is no existing drugs comprising difluocortolone valerate in the form of topical sprays. There is not any combined composition consisting of isoconazole nitrate and difluocortolone valerate used as spray.

Summary of Invention

The invention provides a pharmaceutical composition in the form of topical spray comprising:

a) a glucocorticoid or pharmaceutically acceptable salts, enantiomers, solvates thereof,

b) an antifungal or pharmaceutically acceptable salts, enantiomers, solvates thereof,

(c) at least one pharmaceutically acceptable excipient.

In one aspect the present invention relates to topical administration comprising difluocortolone valerate, isoconazole nitrate and one or more pharmaceutically acceptable excipient, to a patient for treatment of inflammatory or eczematous skin conditions which are accompanied by fungal infection.

The composition may further contain one or more pharmaceutically acceptable excipients. The composition can be in the form of an ointment, cream, lotion, solution or gel. Suitable pharmaceutically acceptable excipients for the topical composition include, but are not limited to, solvents, vehicles, ointment/cream bases, emulsifiers, preservatives, buffers, emollients, humectants, surfactants, and transport enhancers or mixtures there of.

In one embodiment, active ingredients and excipients are mixed to form a sprayable topical formulation.

Detailed Description of Invention

The invention discloses novel pharmaceutical combinations and methods for the treatment or prevention of inflammatory or eczematous skin conditions which are accompanied by fungal infection.

This invention relates to a glucocorticoid and an antifungal pharmaceutical preparation for external use having percutaneous absorption and applicability.

Topical pharmaceutical composition, characterized in that it comprises:

a) a glucocorticoid or pharmaceutically acceptable salts, enantiomers, solvates thereof,

b) an antifungal or pharmaceutically acceptable salts, enantiomers, solvates thereof,

in combination with at least one pharmaceutically acceptable excipient.

A topical pharmaceutical composition, characterized in that it comprises:

a) therapeutically effective amount of difluocortolone or its pharmaceutically acceptable salts, enantiomers, solvates thereof,
b) therapeutically effective amount of isoconazole or its pharmaceutically acceptable salts, enantiomers, solvates thereof,

in combination with at least one pharmaceutically acceptable excipient.

Liquid form preparations include solutions, suspensions and emulsions. Liquid preparations can be formulated in solution in polyethylene glycol and/or propylene glycol, which may contain water and/or alcohol. Solutions suitable for oral use can be prepared by adding the active component in water and/or alcohol and adding suitable colorants, flavors, stabilizing, sweetening, solubilizing and thickening agents as desired. Aqueous suspensions can be made by dispersing the finely divided active component in water with viscous material, i.e., natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose and other well-known suspending agents.

In one aspect, the components of the pharmaceutical composition according to the present invention are brought together into a spray for topical administration according to standard practice and procedures well known to one of ordinary skill in the art using conventional formulation and manufacturing techniques.

In one embodiment, the amount of glucocorticoid agent preferably difluocortolone valerate in this pharmaceutical composition with respect to the total amount interval can be changed. Preferably, difluocortolone valerate is in the amount of 0.01-1 % w/w, more preferably about 0.1 % w/w by weight based on the total weight of the composition.

In another embodiment, the amount of antifungal agent preferably isoconazole nitrate in this pharmaceutical composition with respect to the total amount interval can be changed. Preferably, isoconazole nitrate is in the amount of 0.1-5 % w/w, more preferably about 1 % w/w by weight based on the total weight of the composition.

In one embodiment, the composition is sprayable solution.

In one embodiment, a topical spray composition characterized in that it comprises:

a) difluocortolone or pharmaceutically acceptable salt or ester thereof,
b) isoconazole or pharmaceutically acceptable salts thereof,

in combination with at least one pharmaceutically acceptable excipient.

In one embodiment, a topical spray composition comprises:

a) difluocortolone valerate,
b) isoconazole nitrate,

in combination with at least one pharmaceutically acceptable excipient.

In one embodiment, a process for preparing spray composition comprising:
a) adding propylene glycole in a tank,
b) adding difluocortolone valerate and isoconazole nitratewhile stirring,
c) adding water to the mixture of step(b) while stirring until clear solution,
c) the mixture is made up volume with purified water.

In another embodiment, a process for preparing spray composition comprising:
a) adding propylene glycole in a tank,
b) adding difluocortolone valerate and isoconazole nitrate while stirring,
c) adding ethanol to the mixture of step(b) while stirring until clear solution,
c) the mixture is made up volume with ethanol.

In another embodiment, a process for preparing spray composition comprising:
a) adding propylene glycole in a tank,
b) adding difluocortolone valerate and isoconazole nitrate while stirring,
c) adding isopropyl alcohol to the mixture of step(b) while stirring until clear solution,
c) the mixture is made up volume with isopropyl alcohol.

Advantages

The present invention provides pharmaceutical composition comprising combination of said active ingredients characterized by
a) Stability is enhanced for these substances adversely affected by oxygen and or moisture,
b) Simple and also competitive manufacturing process,
c) Enhanced patient compliance and convenience,
d) It is advantageous when a rapid onset of action is needed,
e) The product is administered easily and quickly,
f) A dose can be removed with out contamination of materials,
g) When sterility is an important factor, it can be maintained while a dose is being dispensed,
h) Rapid onset of action, avoidance of degradation of the drug in the GIT and first pass effect,
i) Lower dose of drug can be used and hence minimize adverse and side effects,
j) Medication can be delivered directly to the affected area in a desired form,

k) Irritation produced by the mechanical application of topical medication is reduced or eliminated,
l) Application of medication in thin layer.

The present invention provides topical drug delivery systems which release a therapeutically effective amount of one or more active pharmaceutical ingredients to the site of absorption or action.

The success of a dermotological drug depends on the ability of the drug to penetrate through skin in sufficient quantities to achieve the desired therapeutic effect.

Another object of the present invention is to increase the rate of percutaneous penetration, thereby shortening the time period in which the active agents can show their effect.

It is obvious that difluocortolone valerate and isoconazole nitrate may be used more effectively, comparing with single activity of difluocortolone valerate and with an enhancement of the activity of difluocortolone valerate due to possible fungal infection, so as to provide a pharmaceutical form for the desired therapeutic effect.

The present invention shows well physical properties in the formulation depends on its solubility characteristics in appropriate excipients for topical formulations. It shows good properties on rheology, particle or droplet size, pH, and visual appearance to provide basic physical stability.

The present invention may be used for the treatment of inflammatory or eczematous skin conditions which are accompanied by fungal infections.

Some of pharmaceutical compositions may comprise alcohol or alcohol derivatives in formulations. If it is not used in pharmaceutical composition, it can be provide less irritation on skin.

Terms

In this invention, the term “glucocorticoid” means a compound including, but not limited to: cortisol, cortisone, corticosterone, dexamethasone, prednisolone, diflucortolone, hydrocortisone, methylprednisolone, fluticasone, prednisone, triamcinolone, diflorasone and pharmaceutically acceptable salts, enantiomers, solvates thereof.

In this invention, the term “antifungal” means a compound including, but not limited to: polyenes (e.g., Natamycin, Nystatin, or the like), allylamines (e.g., Naftifine, Terbinafine, or the like), imidazoles (e.g., Isoconazole, Bifonazole, Chlotrimazole, Econazole, Fenticonazole, Ketocanazole, Miconazole, Oxiconazole, or the like), triazoles (e.g., Fluconazole, Itraconazole, Terconazole, or the like), tolnaftate, ciclopirox, morpholines (e.g., amorolfine or the like), griseofulvin and pharmaceutically acceptable salts, esters thereof.

The term "topical" as used herein is meant to encompass any condition, disease or disorder manifested on body surfaces such as the skin or mucosal membranes; such as the vagina,

anus, throat, eyes and ears, including any tissue covering a body of a mammalian subject consisting of the outer, thinner epidermis (epithelial tissue) and the inner, thicker dermis (connective tissue), that is anchored to the subcutaneous layer. It should be noted that a composition or kit of the invention is intended for dermatological use on any type of skin area, being an exterior exposed area (such as for example areas of the skin, scalp, hair, and nails), an interior skin area such as a mucosal membrane (such as for example mucosal membrane around and on the nostrils, the lips, the ears, the genital area, and the anus) or any vicinal areas in close proximity with the treated skin or mucosal membrane areas wherein said composition and agents comprised in said composition may reach via any kind of diffusion mechanisms to a skin area or mucosal membrane.

Pharmaceutical composition of the present invention may comprise one or more pharmaceutically acceptable excipient(s). Pharmaceutically acceptable excipients comprise, but are not limited to, polymers, solvents, pH adjusting agents, preservatives, fragrances, stabilizers, penetration enhancers, moisturizers,and mixtures thereof.

Polymers can be selected from the group, but are not limited to, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, ethyl cellulose, hydroxypropylmethyl cellulose phthalate, hydroxymethylethylcellulose phthalate, cellulose acetate phthalate, hydroxypropylmethyl cellulose acetate succinate, cellulose acetate maleate, cellulose acetate phthalate; methacrylic polymers, aminoalkyl methacrylate copolymer, methacrylic acid copolymer, polypropylene glycol, polyethylene glycols (PEG) as macrogol or cetomacrogol, polyvinyl acetate phthalate and polyvinyl alcohol, and other materials known to one of ordinary skill in the art. A mixture of polymers may also be used.

Preservatives can be selected from the group, but not limited to, methylparaben and propylparaben and the salts thereof (e.g. sodium or potassium salts), sodium benzoate, citric acid, glycerin, benzoic acid,propyl gallate, propyl paraben, sodium nitrate, hydroxybenzoate, propionic acid, sodium propionate,diazolidinyl urea, phenoxyethanol, DMDM hydantoin,benzyl alcohol, formaldehyde, triclosan, methylisothiazolinone, methylchloroisothiazolinone,butylated hydroxytoluene, propylene glycol, organic acids, esters of parahydroxybenzoic acid(methyl, ethyl, propyl and butyl esters of parahydroxy benzoic acid, and their sodium salts etc), sorbic acid and sodium sorbate, butylated hydroxytoluene and butylated hydroxyanisole, and other materials known to one of ordinary skill in the art. A mixture of preservatives may also be used.

Fragrances can be selected from groups, but are not limited to, esters, amines, terpenes, aromatics, such as menthol, acetaldehyde, fructone, acetoin, furaneol, isoveraldehyde, vanilin, anisole, terpineol and other materials known to one of ordinary skill in the art. A mixture of fragrances may also be used.

Stabilizers can be selected from the group, but are not limited to, α-Tocopheryl acetate, acetylcysteine, ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), cysteine, cysteine hydrochloride, d-α-Tocopherol, dithiothreitol, monothioglycerol, nordihydroguaiaretic acid, propyl gallate, sodium bisulfite, sodium

formaldehyde, sodium metabisulfite, sulfoxylate, sodium sulfite, sodium thiosulfate and thiourea and other materials known to one of ordinary skill in the art, and mixtures thereof.

pH adjusting agents can be selected from the group, but are not limited to, triethanolamine, triethylamine, diethylmethylamine, ethyldimethylamine, isopropyldimethylamine, adipic acid, glycine, citric acid, calcium hydroxides, magnesium aluminometasilicates, buffers, typically Bronsted-Lowry and/or Lewis acids and/or bases, or any combinations thereof and other materials known to one of ordinary skill in the art.

Moisturizers can be selected from the group, but are not limited to, polyethylene glycol, propylene glycol, dipropylene glycol, 1,3-butylene glycol, glycerin, diglycerin, xylitol, maltitol, maltose, D-mannitol, glucose, fructose, sodium chondroitin sulfate, sodium hyaluronate, sodium lactate, glucosamine, cyclodextrin, cococaprylate/caprate and other materials known to one of ordinary skill in the art and mixtures thereof.

Solvents can be selected from the group, but not limited to, ethyl alcohol, polyethylene glycol, propylene glycol, isopropyl alcohol, purified water and other materials known to one of ordinary skill in the art and mixtures thereof.

A process for preparing a topical spray composition comprising:
a) adding propylene glycol in a tank,
b) adding difluocortolone valerate and isoconazole nitrate while stirring,
c) adding water to the mixture of step (b) while stirring until clear solution,
c) the mixture is made up volume with solvent.

Example 1

Spray composition is made of the following components:

Content	**Function**	**Formula % (w/w)**
Isoconazole nitrate	Active Ingredient	1,00
Difluocortolone valerate	Active Ingredient	0,10
Propylene glycol	Solvent	25,0
Ethanol 95 %	Solvent	QS

Example 2

Spray composition is made of the following components:

Content	Function	Formula % (w/w)
Isoconazole nitrate	Active Ingredient	1,00
Difluocortolone valerate	Active Ingredient	0,10
Propylene glycol	Solvent	80,0
Purified water	Solvent	QS

Example 3

Spray composition is made of the following components:

Content	Function	Formula % (w/w)
Isoconazole nitrate	Active Ingredient	1,00
Difluocortolone valerate	Active Ingredient	0,10
Propylene glycol	Solvent	25,0
Isopropyl Alcohol (IPA)	Solvent	QS

Claims

1. A topical spray composition, characterized in that it comprises:

a) difluocortolone or pharmaceutically acceptable salt or ester thereof,
b) isoconazole or pharmaceutically acceptable salts thereof,

in combination with at least one pharmaceutically acceptable excipient.

2. A topical spray composition according to claim 1, wherein it comprises difluocortolone valerate.

3. A topical spray composition according to claim 2, wherein difluocortolone valerate is in the amount of 0.01-1 % w/w, preferably about 0.1 % w/w by weight based on the total weight of the composition.

4. A topical spray composition according to claim 1, wherein it comprises isoconazole nitrate.

5. A topical spray composition according to claim 4, wherein isoconazole nitrate is in the amount of 0.1-5 % w/w, preferably about 1 % w/w by weight based on the total weight of the composition.

6. A topical spray composition according to any of the preceding claims, further comprising at least one solvent selected from the group consisting of propylene glycol, water, ethanol and isopropyl alcohol.

7. A topical spray composition according to any of the preceding claims, for use in the treatment of inflammatory skin conditions such as eczema and dermatitis, and also relieving the symptoms of a flare-up, itching and redness,which are accompanied by fungal infection.

8. A process according to any of the preceding claims for preparing a topical spray composition comprising:
a) adding propylene glycol in a tank,
b) adding difluocortolone valerate and isoconazole nitrate while stirring,
c) adding water to the mixture of step (b) while stirring until clear solution,
c) the mixture is made up volume with solvent.

INTERNATIONAL SEARCH REPORT

International application No
PCT/TR2015/050208

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K9/12 A61K31/4174 A61K31/573 A61P17/00
A61P31/10
ADD.
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 A61P

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 practicable, search terms used)
EPO-Internal, CHEM ABS Data, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	VERALDI STEFANO: "Isoconazole nitrate: a unique broad-spectrum antimicrobial azole effective in the treatment of dermatomycoses, both as monotherapy and in combination with corticosteroids", MYCOSES, vol. 56, no. Suppl. 1, Sp. Iss. SI, May 2013 (2013-05), pages 3-15, XP002755043, page 9 - page 12	1-8

-/--

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

[X] 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

"E" earlier application or patent 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

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 March 2016	18/03/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Pacreu Largo, Marta

1

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/TR2015/050208

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	HAVLICKOVA B ET AL: "The advantages of topical combination therapy in the treatment of inflammatory dermatomycoses", MYCOSES, WILEY-BLACKWELL PUBLISHING LTD, GB, vol. 51, no. Suppl. 4, 1 September 2008 (2008-09-01), pages 16-26, XP008122342, ISSN: 0933-7407 page 20 - page 21	1-8
Y	HERMS E ET AL: "[Once daily administration of isoconazole as a cream, solution and spray: comparative studies of patients with dermatomycoses].", ZEITSCHRIFT FÜR HAUTKRANKHEITEN 15 MAY 1988, vol. 63, no. 5, 15 May 1988 (1988-05-15), pages 377-384, XP009188847, ISSN: 0301-0481 page 383 - page 384	1-8
Y	WO 2015/138650 A1 (PROMIUS PHARMA LLC [US]) 17 September 2015 (2015-09-17) pages 12,44; claim 1	1-8
Y	WO 2011/026076 A2 (REDDYS LAB LTD DR [IN]; REDDYS LAB INC DR [US]; UBAIDULLA UDHUMANSHA [] 3 March 2011 (2011-03-03) page 11; claims; examples	1-8

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/TR2015/050208

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2015138650 A1	17-09-2015	US 2015258119 A1	17-09-2015
		WO 2015138650 A1	17-09-2015
WO 2011026076 A2	03-03-2011	EP 2473161 A2	11-07-2012
		JP 5833007 B2	16-12-2015
		JP 2013503203 A	31-01-2013
		US 2012214776 A1	23-08-2012
		WO 2011026076 A2	03-03-2011