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CA 2986295 A1 2017/01/19

(21) 2 986 295

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

(86) Date de dépôt PCT/PCT Filing Date: 2015/07/10
(87) Date publication PCT/PCT Publication Date: 2017/01/19
(85) Entrée phase nationale/National Entry: 2017/11/17
(86) N° demande PCT/PCT Application No.: EP 2015/065840
(87) N° publication PCT/PCT Publication No.: 2017/008831

(51) Cl.Int./Int.Cl. *A61K 45/06* (2006.01),
A61K 33/00 (2006.01), *A61P 17/00* (2006.01),
A61P 17/02 (2006.01), *A61P 17/12* (2006.01)

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(54) Titre : UTILISATION D'HYDROXYDE DE POTASSIUM DANS LE TRAITEMENT DE LA KERATOSE ACTINIQUE
(54) Title: USE OF POTASSIUM HYDROXIDE IN THE TREATMENT OF ACTINIC KERATOSIS

(57) Abrégé/Abstract:
The present invention relates to the use of potassium hydroxide (KOH) in a pharmaceutically acceptable form (agent), and to compositions, respectively comprising potassium hydroxide (KOH), respectively, for the dermal treatment of actinic keratosis.

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 January 2017 (19.01.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/008831 A1

(51) International Patent Classification:
A61K 45/06 (2006.01) *A61P 17/12* (2006.01)
A61K 33/00 (2006.01) *A61P 17/02* (2006.01)
A61P 17/00 (2006.01)

(21) International Application Number:
PCT/EP2015/065840

(22) International Filing Date:
10 July 2015 (10.07.2015)

(25) Filing Language: English

(26) Publication Language: English

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(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 2017/008831 A1

(54) **Title**: USE OF POTASSIUM HYDROXIDE IN THE TREATMENT OF ACTINIC KERATOSIS

(57) **Abstract**: The present invention relates to the use of potassium hydroxide (KOH) in a pharmaceutically acceptable form (agent), and to compositions, respectively comprising potassium hydroxide (KOH), respectively, for the dermal treatment of actinic keratosis.

Use of potassium hydroxide in the treatment of actinic keratosis

Technical field

The present invention relates to an agent of potassium hydroxide (KOH), specifically in a pharmaceutically acceptable composition, especially compositions in the form of or comprising an aqueous solution of potassium hydroxide (KOH), as the active ingredient, for the therapeutic, especially topical dermal use in the treatment of actinic keratosis.

Back ground

Actinic keratosis is a condition of damage of the upper cornea layer induced by light, especially sun light (UV-radiation). Typical symptoms are scaly, or crusty patches of skin especially of the skin of the face, the forehead, the neck, the hands and the nose. Usually the damage progresses slowly, however after a longer period of time it can also turn into a specific kind of cell carcinoma, the so called squamous cell carcinoma. In general actinic keratosis is known as a hyper proliferative condition of the skin material related to an increased cell growth.

Most frequently actinic keratosis occurs on areas of white fair skinned people having less pigmented skin especially in the age of 50 years and more, who are often exposed to sun light either because of their working area or due to increased outdoor activities .

A general summary of common treatment methods of actinic keratosis is published by WILLIAM J. MCINTYRE ET AL: "Treatment Options for Actinic Keratoses", American Family Physician , vol. 76, no. 5 2007, pages 667-671, XP002667-626, (URL:http://www.aafp.org/afp/2007/0901/p667.html). As can be seen, there are different methods of treatment such as surgical (ablative) methods (cryosurgery, electrotherapy, photodynamic therapy using 5-aminolevulinic acid) as well as topical dermal treatments. Topical treatments include the use of creams, gels or ointments comprising active agents such as fluorouracil, diclophenac , imiquimod, or hyaluronic acid in combination with the aforementioned active ingredients. However such treatments may lead to crusty or scaly skin areas.

State of the art

WO 2011/126539 A2 is related to the use of extracts of hamelia patens extract in the treatment of various skin disorders for example actinic keratosis.

EP 2 079 525 A1 discloses the use of deuterium dioxide in the treatment of conditions related to hyper proliferative disorders such as several keratoses. In one embodiment patches or bandages, creams or gels are used. Thereby the increased skin cell proliferation shall be reduced. It is assumed that deuterium oxide inhibits the mitotic cell cycle (cell division) and that hyper proliferative cells collect more deuterium oxide than normal proliferative cells.

EP 2 620 146 A1 suggests the use of ibuprofen in the topical (dermal) treatment of actinic keratosis. Suitable compositions are creams, gels or ointments.

WO 2013/079211 (EP 2 785 336) is related to the use of polyoxylated long chain fatty alcohols (macrogols) such as polidocanol (C_{12} (7-11) polyethoxylated dodecanol). Suitable application forms are creams, gels, micro emulsions, trans dermal application forms or epicutaneous injections. The amount of the active ingredient (polidocanol) is depending on the mode of application (topical-dermal or trans dermal or injection) and may be in the range of up to 30 g. An in vivo activity has not been shown.

In view of the period of effectiveness of an active ingredient when used topically or in a dermal mode it should at first be considered to apply a pharmaceutical active agent without incurrence of undesired side effects. Furthermore, in this connection a selective application of the active ingredient to the desired area to be treated is important as well.

Moreover, systemic actions being possible by the aforementioned application forms such as trans dermal-diffusive deliverance or by injections and/or local excess of dosage may not be favorable.

In addition an accumulation of the active ingredient in the skin area to be treated should be avoided.

Object of the invention

The object of the present invention is the provision of an agent and an easily produced composition, respectively useful in the local treatment of actinic keratosis whereby a systemic accumulation of the active ingredient or a direct accumulation of the active agent in the skin area to be treated may essentially be avoided. On the other hand the use of such an agent or composition should cause a considerable, especially rapid healing reaction thereby allowing a repeated application. In addition the avoidance of serious side effects related to the active ingredient in the skin area to be treated were favorable.

Solution of the object

The above object/s is/are solved by the provision and use of an agent of potassium hydroxide (KOH), specifically in a pharmaceutically acceptable composition, and to compositions, respectively comprising or specifically consisting of an aqueous solution comprising potassium hydroxide (KOH), preferably as the main active agent, in an indication related suitable amount of e.g. of about from 0.01 up to 15 wt. %, especially of from 0.1 up to 10 wt. % and most favorably in an amount of from 0.1 up to 5 wt. %, each related to the total amount (wt. %) of the composition.

Such pharmaceutically acceptable KOH and such pharmaceutically acceptable solutions comprising potassium hydroxide (KOH) are known in the art and may easily be prepared, respectively by admixture of water and potassium hydroxide or by dilution of a pre-prepared commercially available solution. Such solutions are alkaline, preferably exhibiting a pH value of between 8 and 15, more preferably of 9,5 to 15 and most preferred of 13 to 15.

The active agent and the composition, respectively, comprising the same may be applied by spraying , droping, spreading onto the area to be treated.

Preferably the area to be treated is selected from the skin, especially the skin of/on the scalp, head, the skin within the face, the neck, the nose, the skin of the hands and arms/forearms as well as on the decoltée, and combinations thereof.

Optionally further additives may be incorporated into the composition used according to the invention, e.g. in an amount/concentration of from 0.01 to 5 wt.% , related to the total amount of the composition (wt.%).

Such further additives may be selected from the group comprising surface active agents such as non ionic surfactants, especially those having a HLB- value of from 9 to 20 having O/W properties. Such surfactants are C_1-C_{15} - alkyl- C_{8-22-} fatty alcohol ethers or C_1-C_{15}- alkyl- C_{12-22-}fatty acid esters, or (poly)oxylated - C_{8-22-} fatty alcohols and (poly) oxylated C_{8-22-} fatty acid esters, especially C_{10}-C_{18}-fatty alcohols or (poly)ethoxylated and/or –(poly)-propoxylated derivatives thereof (= fatty alcohol ethoxylates and/or – propoxylates) having a degree of ethoxylation (EO) and/or propoxylation (PO), respectively of 8-25, or mixtures thereof. Specific representatives of such compounds are e.g. laureth (9) (hydroxypoly-ethoxydodecane = macrogollaurylether (9)) or polyoxyethylated cetyl and/or stearylether such as polyoxyethylated (20) or (25) cetylstearylether (Ceteareth (20) or (25)) or polyoxyethylen(10) or 820) cetylether (Ceteth(10) or (20)) or polyoxyethyled (10) stearylether (Steareth (10)). or polyoxyethyled (10) oleylether (Oleth(10)).

Further examples of non ionic surfactants are non ionic glucosides such as esters and ethers of glucose, methyl glucose or saccharose and saturated and/or partially unsaturated C_{12-22}- fatty acids or C_{8-22-}fatty alcohols, polyoxyethylated and/or polyoxypropylated sugar esters or sugar ethers of C_{12}-C_{18} fatty acids and C_{12}-C_{18} fatty alcohols having an EO- and PO- degree, respectively of 8-25.

Surfactants may be present in an amount of from 0.01 to 3 wt. %, preferably from 0.1 to 2 wt. %, especially of from 0.5 to 1.8 wt. %, related to the total amount of the composition.

In a specific embodiment the agent or composition according to the invention may further comprise as additive/s 0,1 to 2 wt.% of one or more non ionic surfactants having an HLB (hydrophilic-lipophilic balance) value of 12-18, especially C_{10}-C_{18}-fatty alcohols or (poly)ethoxylated and/or –(poly)-propoxylated derivatives thereof as described above.

Further optional additives may be selected from preservatives such as alcohols, or macro-molecular additives such as geling agents, or salts, especially to assure the pharmacological properties of the solution comprising potassium hydroxide, in relation to its concentration.

In general such additives are not necessary und preferably not be comprised by the pharmaceutically acceptable agent and compositions of potassium hydroxide (KOH), especially the respective aqueous composition used according to the present invention.

Especially, in specific cases geling agents such as hydroxyl propyl cellulose or polyacrylates are not necessary within the agent/composition used according to the present invention and are therefore preferably not comprised therein when no geling agent is desired.

In a preferred embodiment an aqueous solution comprising potassium hydroxide, especially consisting of water and potassium hydroxide, in an amount of 3 to 7 wt. %, especially 5 wt. % KOH, related to the total amount of the composition, and preferably comprising no further additives, is used according to the invention in the treatment of actinic keratosis.

In another preferred embodiment an aqueous solution comprising potassium hydroxide, especially comprising potassium hydroxide in an amount of 3 to 7 wt. %, preferably 5 wt. %, as well as 0.1 to 2 wt. % , each related to the total amount of the composition, of one or more non ionic surfactants having an HLB value of 12 to 18 is used according to the invention in the treatment of actinic keratosis.

The agent/composition of and used, respectively according to the invention comprises potassium hydroxide (KOH) as the pharmaceutically active ingredient, preferably as the sole (main) active ingredient in the desired amount and water (aqueous solution). Further known active agents related to the same indication (actinic keratosis) such as ibuprofen, fluorouracil, diclophenac, deuterium dioxide, imiquimod (4-Amino-1-isobutyl-

1*H*-imidazo[4,5-*c*]chinolin), hamelia (patens) extract, or other keratinolytically active agents such as vitamin-A-acid or salicylic acid and/or the pharmaceutically acceptable derivatives thereof or combinations thereof or with aforementioned agents may be included in the compositions of and used according to the invention if necessary or desired for any reason. Such further known active ingredients, especially as mentioned above, however are usually not necessary and the present agent/aqueous compositions with potassium hydroxide (KOH) according to the invention do preferably not comprise such further active agents.

Specifically the agent/composition as used according to the invention is preferably free of further agents being active in regard to actinic keratosis, selected from the group consisting of diclophenac, deuterium dioxide, fluorouracil, imiquimod, Hamelia (patens)- extract or combinations thereof or therewith.

On the other hand it is possible to omit higher amounts e.g. more than 3 wt. %, of polyoxylated fatty alcohols specifically such as pegylated (7-11-polyethylenglykol)- C_{12-16}- fatty alcohol ethers (macrogols) such as polyoxy(ethoxylated (9) -C_{12}- fatty alcohol (hydroxypolyethoxy (7-11)-dodecane) in amounts possibly being pharmaceutically active in relation to actinic keratosis.

The compositions/agent of and used according to the present invention may however comprise lower amounts thereof (polyoxylated fatty alcohols as described above), e. g. up to 2.5 wt. % (e.g. 0.1 to 2 wt. %, or 1 to 1.8 wt. %) in relation to the total amount of the composition.

The present invention is also related to the application of an agent or more preferably to a composition consisting of potassium hydroxide (KOH) and water, especially water purified for pharmaceutical application, wherein potassium hydroxide is present in an amount of from 0.1 to 10 wt. %, preferably 0.5 to 5 wt. %, especially in an amount of 5 wt. %.

The composition/agent may be applied onto the skin area by delivering the same from a suitable application bottle which may reversibly be opened/closed, especially

in connection with suitable application means such as swab, spatula, or others. It is also possible to use dosage or spray devices or other application forms known to the man skilled in the art.

The composition or agent of or used according to the invention may be used in the form of a pharmaceutical or a medical product.

A medical product according to the invention means a product, composition or device comprising such compositions or products, the main activity thereof in or on the human body neither being provided by pharmacological or immunological means nor by metabolic action, however the action thereof may be supported thereby.

A pharmaceutical agent and a pharmaceutically active agent/composition, respectively according to the invention especially means substances or compositions of substances or devices comprising such substances/compositions determined for the use in or on the human body in order to act on or correct the physiological functions by a pharmacological, immunological or metabolic action.

In order to apply the composition/agent according to the invention it may be comprised in an application product, especially in a medical or pharmaceutical product, preferably consisting of an aqueous solution comprising potassium hydroxide (KOH), specifically in an amount of from 0.1 to 10 wt. %, more preferably 0.5 to 5 wet. %, and most preferred in an amount of 5 wt. % as the active ingredient, in the treatment of actinic keratosis, together with an applicator device for specific (dermal) application of the (fluid) aqueous composition to the skin of the human body in need thereof whereby the application device comprises a container comprising the fluid composition/agent exhibiting a reversible cap and a suitable outlet enabling the deliverance of the fluid composition/agent.

Mode / kind of application

In accordance with the present invention the agent or composition as indicated is applied to the skin area in need of a treatment by dropping, spraying, spreading using a suitable applicator device such as a painting. The amount of the active agent needed is depending on the size, color, deepness of the lesion/ skin damage and may optionally be determined by a skilled man and/or a physician. The application dosage may vary from e.g. 0.1. to 10 drops or from 0.01 to 0.5 ml/ application rate. Consequently about some square millimeters to some square centimeters of the lesions of the skin area to be treated will be covered. Thereby an improvement of the condition is achieved in a surprisingly rapid mode.

As patients mammals, especially humans in a condition of need of a treatment as described herein are eligible. The composition as used according to the invention are preferably related to human beings.

According to the invention the skin area exhibiting actinic keratosis is obviously stimulated for rapid reaction. Without being bound to a specified theory it may be assumed that the initial irritation based on the alkaline milieu initiates a physical abrasive removal of the plaques, bumps or maculae thereby helping improving the normalization of cell proliferation of the skin cells affected.

Within the sense of the present invention actinic keratosis means a hyper proliferative condition or disease of non- but potentially premalignant kind, which however under certain conditions may progress into a malignant state. The treatment of actinic keratosis is consequently recommended and important in order to avoid such malignancy and metastasis and therefore may be a suitable means of the prevention thereof.

The above disease is in contrast to other skin disorders such as inflammatory diseases like dermatitis, psoriasis or sun burn, which may be related to an acidosis which is not the case in a keratosis related condition. It was therefore highly surprising that such non-acidic conditions may be treated using an alkaline agent or solution without the occurrence of serious side effects.

Preparation of the agents/compositions

Pharmaceutically acceptable KOH and pharmaceutically acceptable solutions comprising potassium hydroxide (KOH) and a carrier are known in the art and may easily be prepared, respectively by admixture of water which then is the carrier and potassium hydroxide or by dilution of a pre-prepared commercially available solution. Such solutions are alkaline, preferably exhibiting a pH value of between 8 and 15, more preferably of 9,5 to 15 and most preferred of 13 to 15. As far as desired one or more additives as aforementioned may be added under agitation. The resulting fluid may then be filled into suitable containers as known in the art.

Examples

The invention is further illustrated by the following non-limiting examples.

Example 1: Preparation of a KOH composition 1

A composition for use according to the invention is prepared by solving 5 g of potassium hydroxide PH. Eur. in 100 ml water (purified for pharmaceutical purposes) in a manner known per se. The solution is subsequently filled into a suitable container. A sterile filling is not necessary because of the high alkaline pH value of 14.

Example 2: Preparation of a KOH composition 2

A composition for use according to the invention is prepared by solving 3 g of potassium hydroxide PH. Eur. in 100 ml water (purified for pharmaceutical purposes) in a manner known per se. Subsequently 0,6 wt.% , related to the total amount of the composition , of Ceteareth(25) is added under agitation. Then the clear fluid solution is filled into a suitable container. A sterile filling is not necessary because of the high alkaline pH value of 13,5.

Example 3: Application of a composition according to the invention

34 patients (21 male, 13 female, mean age about 68) affected by actinic keratosis did apply twice a day during a period of 15 days a composition according to example 1 by spreading it in an amount sufficient to cover the respective skin area in the face and in some cases on the body as well. If necessary the application was repeated.

After 15 days, 1 month and 12 weeks, respectively the lesions were evaluated by dermoscopy and compared to the initial situation.

Results:

79,4 % of the patients showed a complete resolution of the target treated lesion, 35.3 % after the first treatment cycle and 44.1 % after 2 cycles. None of the treated lesions showed recurrence. No serious side effects were observed.

Claims

1. Agent in the form of potassium hydroxide (KOH) in a pharmaceutically acceptable composition for the use in the dermal treatment of actinic keratosis.

2. Agent according to claim 1 characterized in that the composition is an aqueous solution of potassium hydroxide (KOH) for the use in the treatment of actinic keratosis.

3. Agent or composition according 2 characterized in that it is alkaline.

4. Agent or composition according to any of claims 1 to 3 for use in the topical application to the skin of/on the scalp, within the face, the neck, the nose, the skin of the hands and arms/forearms as well as on the decoltée, and combinations thereof.

5. Agent or composition according to any of claims 1 to 4 for use in the topical application by spraying, spreading, droping onto the skin area to be treated.

6. Agent or composition according to any of claims 2 to 5 characterized in that it comprises besides water potassium hydroxide, the latter one in an amount of 0,1 to 10 wt.%, related to the total amount of the composition.

7. Agent or composition according to any of claims 2 to 6 characterized in that the pH value of the composition is between 13 and 15.

8. Agent or composition according to any of claims 2 to 7 characterized in that it further comprises as additive/s 0,1 to 2 wt.% of one or more non ionic surfactants having an HLB value of 12-18.

9. Agent or composition according to any of claims 2 to 7 characterized in that it consists of water and potassium hydroxide the latter one in an amount of 0,1 to 10 wt.%, related to the total amount of the composition.

10. Agent or composition according to any of claims 1 to 9 characterized in potassium hydroxide (KOH) is the main active agent.

11. Agent or composition according to any of claims 1 to 10 characterized in that is in the form of a medical product or in the form of a pharmaceutical product.

12. Use of potassium hydroxide (KOH) in a pharmaceutically acceptable carrier for preparing a composition for the dermal treatment of actinic keratosis.

13. Use according to claim 12 characterized in that the composition is an aqueous alkaline solution of potassium hydroxide having a pH value of about 12 to 15.

14. Use according to any of claims 12 or 13 for the topical treatment of actinic keratosis of the skin of/on the scalp, within the face, the neck, the nose, the skin of the hands and arms/forearms as well as on the decoltée, and combinations thereof of human beings.

15. Use according to any of claims 12 to 14 characterized in that the composition comprises besides water potassium hydroxide the latter one in an amount of 0,1 to 10 wt.%, related to the total amount of the composition.

16. Use according to any of claims 12 to 14 characterized in that the composition consists of water and potassium hydroxide the latter one in an amount of 0,1 to 10 wt.%, related to the total amount of the composition.