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(54) Title: METHOD OF TREATING ACNE

(57) Abstract: The present disclosure relates to a method of treating acne wherein said method comprises applying topically an effective amount of stable substantially aqueous composition comprising from about 0.001% to about 1.5% of isotretinoin by total weight of the composition. The present disclosure also relates to stable substantially aqueous topical composition comprising isotretinoin and a viscosity-enhancing agent. The present disclosure further relates to stable substantially aqueous topical composition comprising isotretinoin in combination with another anti-acne agent.

METHOD OF TREATING ACNE

Field of the Invention

The present disclosure relates to a method of treating acne, the method comprising applying topically an effective amount of stable substantially aqueous composition comprising from about 0.001% to about 1.5% of isotretinoin by total weight of the composition. The present disclosure also relates to a stable substantially aqueous topical composition comprising from about 0.001% to about 1.5% of isotretinoin by total weight of the composition. In some embodiments, the composition comprises a viscosity-enhancing agent. The present disclosure further relates to stable substantially aqueous topical composition comprising isotretinoin in combination with a second anti-acne agent.

Background of the Invention

Acne is a skin disorder which can be treated through oral as well as topical administration of drugs. Isotretinoin, also known as 13-cis retinoic acid, has been prescribed orally for the treatment of severe forms of acne. However, isotretinoin is believed to have a very high teratogenic potential. Thus, this drug is generally only prescribed by or under the supervision of a dermatologist. Though the oral treatment is generally thought to be more effective against severe forms of acne, topical treatment may be preferred because it may minimize any potential systemic adverse effects.

Since isotretinoin is practically insoluble in water, topical formulations of isotretinoin currently marketed are either alcohol-based or oil-based. For example, the topical gel of isotretinoin marketed in Europe under the brand name “Isotrex” is alcohol-based. U.S. Patent No. 4,843,096 also reports a substantially non-aqueous or alcohol-based gel of isotretinoin. Isotretinoin, being a retinoid, can be an irritant to the skin, and the quick drying effects of alcohol from alcohol-based gels can exacerbate the irritant effects of isotretinoin. As acne itself is associated with increased production of sebum or oil, topically applied oil-based or greasy-formulations can result in reduced patient acceptability.

Summary of the Invention

The present disclosure provides a method of treating acne wherein said method comprises applying topically an effective amount of stable substantially aqueous composition comprising from about 0.001% to about 1.5% of isotretinoin by total weight of

the composition. The present disclosure also relates to stable substantially aqueous topical composition comprising isotretinoin and a viscosity-enhancing agent. The present disclosure further relates to stable substantially aqueous topical composition comprising isotretinoin in combination with another anti-acne agent.

Detailed Description of the Invention

Due to the adverse effects and problems associated with oil- and alcohol-based isotretinoin formulations, applicants developed an effective topical aqueous composition of isotretinoin which is comparatively less irritating to the skin and more acceptable by the patients. The present application provides a stable, substantially aqueous topical composition of isotretinoin which is less irritating to the skin. Further, the present application provides a substantially aqueous topical composition comprising isotretinoin in combination with a second anti-acne agent.

In some embodiments, the present disclosure provides a method of treating acne wherein said method comprises applying topically an effective amount of stable substantially aqueous composition comprising from about 0.001% to about 1.5% of isotretinoin by total weight of the composition.

In some embodiments, the present disclosure provides a stable substantially aqueous topical composition comprising isotretinoin in an amount of about 0.001% to about 1.5% by total weight of the composition, wherein the composition comprises total degradation product of isotretinoin in an amount of less than 2% w/w when stored at a temperature 40°C and 75% RH for a period of at least 3 months. In some embodiments, the composition comprises total degradation products of isotretinoin in an amount of less than 1.5% w/w, less than 1.0% w/w, or less than 0.5% w/w when stored at a temperature 40°C and 75% RH for a period of at least 3 months.

In some embodiments, the composition may further comprise 5,6-epoxy-13-cis retinoic acid in an amount of less than about 2 % w/w based on total weight of the composition. 5,6-epoxy-13-cis retinoic acid is a degradation product of isotretinoin. In some embodiments, the composition comprises 5,6-epoxy-13-cis retinoic acid in an amount of less than 1.5% w/w, less than 1.0% w/w, less than 0.5% w/w when stored at a temperature 40°C and 75% RH for a period of at least 3 months.

In some embodiments, isotretinoin is present in an amount of about 0.001% to about 1.5% by weight of the total composition, about 0.001% to about 1.0% by weight of the total

composition, about 0.005% to about 1.0% by weight of the total composition, about 0.005 % to about 0.5 % by weight of the composition, about 0.01% to about 1.0% by weight of the total composition, about 0.05% to about 1.0%, about 0.05% to about 0.5% by weight of the total composition, or about 0.05 % to about 0.1 % by weight of the total composition.

In some embodiments, the composition is in the form of a solution, suspension, dispersion, spray, cream, lotion, roll-on, dispersion or a gel. In some embodiments, the composition is in the form of a cream or lotion. In some embodiments, the composition is in the form of a gel. In some embodiments, the composition is in the form of a spray. In some embodiments, the composition is in the form of a solution.

In some embodiments, the composition comprises isotretinoin partially in a dissolved form and partially in a suspended form.

In some embodiments, the composition has a viscosity of at least 3000 cps when determined at room temperature (20 °C - 25 °C) using a Brookfield viscometer, e.g., a model DV-E, spindle #2 at 20 revolutions per minute (rpm). In some embodiments, the composition has a viscosity of about 3,000 cps to about 500,000 cps, about 3,000 cps to about 300,000 cps or about 3,000 cps to about 200,000 cps at room temperature (20 °C - 25 °C) as determined by a Brookfield viscometer. In some embodiments, the composition has a viscosity of about 10,000 cps to about 500,000 cps, about 50,000 cps to about 300,000 cps, or about 100,000 cps to about 200,000 cps at room temperature (20 °C - 25 °C) as determined by a Brookfield viscometer.

In some embodiments, the composition comprises a viscosity-enhancing agent. In some embodiments, the composition comprises a viscosity-enhancing agent in an amount of an amount of about 0.05% to about 20% w/w based on the total weight of the composition, in an amount of about 0.2 % to about 10%, or in an amount of about 0.5 % to about 5 % by weight of the total composition. In some embodiments, the composition comprises a viscosity-enhancing agent in an amount of about 0.1% to about 5% by weight of the total composition.

In some embodiments, the viscosity-enhancing agent is selected from the group consisting of gums e.g. karaya gum, locust bean gum, guar gum, xanthan gum, arabic gum, tragacanth gum, carrageenan, pectin, agar, alginic acid, and sodium alginate; cellulosic derivatives, e.g. hydroxypropyl methyl cellulose, hydroxypropyl cellulose, methylcellulose, hydroxyethyl cellulose, sodium carboxymethylcellulose, microcrystalline cellulose,

chitosan, and other synthetic polymers e.g. Carbopol 940, Carbopol 980, Carbopol 974P, Carbopol 971P, Carbopol 934P, methacrylates and polyacrylates; alginic acid-propylene glycol esters; polyoxyethylene-polyoxypropylene copolymers; polyvinyl pyrrolidone; polyethylene glycol; polyethylene oxide; polyvinyl alcohol; silicon dioxide; and mixtures thereof.

In some embodiments, the composition further comprises one or more pharmaceutically acceptable excipients selected from the group consisting of co-solvents, alkalinizers, antioxidants, chelating agents, preservatives, surfactants, penetration enhancers, pH-adjusting agents, humectants, perfumes, and mixtures thereof.

In some embodiments, the composition comprises a co-solvent. In some embodiments, suitable co-solvents can be selected from the group consisting of, but not limited to, diethylene glycol monoethyl ether; dimethyl isosorbide, propylene glycol, polyethylene glycol, and glycerin; fatty acid esters, e.g. isopropyl myristate, isopropyl palmitate, isopropyl stearate, and ethyl oleate; fatty acids, e.g. capric acid, lauric acid, myristic acid, oleic acid and linoleic acid; polyoxyethylene sorbitan esters, e.g. polysorbate 20, polysorbate 40, polysorbate 60, and polysorbate 80; and mixtures thereof. In some embodiments, the amount of co-solvent used in the present disclosure can range from about 10% w/w to about 30% w/w, or from about 10% w/w to about 20% w/w based on the total weight of the composition.

In some embodiments, the composition comprises an alkalinizer. Suitable alkalinizer can be selected from triethanolamine and sodium hydroxide and are present in an amount of at least 0.01 % w/w based on the total weight of the composition. In some embodiments, the alkalinizer is about 0.01% to about 10% w/w, or about 0.1% to about 1% based on the total weight of the composition. In some embodiments, the alkalinizer is selected from the group consisting of triethanolamine and sodium hydroxide, or combinations thereof.

In some embodiments, the composition comprises an antioxidant. Examples of suitable antioxidants include, but are not limited to, butylated hydroxy anisole, butylated hydroxy toluene, sodium metabisulfite, sodium sulfite, ascorbic acid, ascorbyl palmitate, acetylcysteine, propyl gallate, tocopherol, and mixtures thereof. The antioxidants may be present in an amount of at least 0.0001 % w/w based on the total weight of the composition, or about 0.0001% to about 1.0%, about 0.0001% to about 0.1%, or about 0.0001% to about

0.01% w/w based on the total weight of the composition. In some embodiments, the antioxidants are present in an amount of at least 0.001 % w/w based on the total weight of the composition, or about 0.001% to about 1.0%, about 0.001% to about 0.1%, or about 0.01% to about 0.1% w/w based on the total weight of the composition.

In some embodiments, the composition comprises a chelating agent. Examples of suitable chelating agents include, but are not limited to, ethylenediamine tetra-acetic acid or derivatives or salts thereof, e.g. disodium edetate; dihydroxyethyl glycine, glucamine; acids, e.g. citric acid, tartaric acid, gluconic acid, phosphoric acid, and mixtures thereof. The chelating agent may be present in the composition in an amount of at least 0.01 % w/w based on the total weight of the composition, or about 0.001% to about 1%, about 0.01% to about 1%, about 0.01% to about 0.1% or about 0.1% to about 1% w/w based on the total weight of the composition.

In some embodiments, the composition comprises a preservative. Examples of suitable preservatives include, but are not limited to, methyl-, ethyl-, propyl-, or butyl- esters of para-hydroxy benzoic acid or sodium salts thereof, benzyl alcohol, benzoic acid, sodium benzoate, chlorhexedine benzalkonium chloride, potassium sorbate, dichlorobenzyl alcohol, and mixtures thereof may be present in an amount of at least 0.01 % w/w based on the total weight of the composition.

Examples of suitable surfactants include, but not limited to, polyethoxylated fatty acid esters, docusate sodium, polyoxyethylene sorbitan esters, polyoxyethylene hydrogenated castor oil, polyoxyethylene polyoxypropylene glycol, sorbitan esters, sodium lauryl sulphate, nonooxynol, glyceryl monostearate, and mixtures thereof. In some embodiments, the surfactants can be present in an amount of at least 0.01 % w/w based on the total weight of the composition, or about 0.001% to about 1%, about 0.01% to about 1%, about 0.01% to about 0.1% or about 0.1% to about 1% w/w based on the total weight of the composition.

Examples of suitable penetration enhancers include, but not limited to, dimethyl sulfoxide (DMSO), dimethyl acetamide, dimethyl formamide; ethers, e.g., diethylene glycol monoethyl ether (Transcutol®); surfactants, e.g., sodium laurate, sodium lauryl sulfate, polysorbates; alkyl glycosides; benzyl alcohol; fatty acids, e.g., lauric acid, oleic acid, valeric acid, and isostearic acid; fatty acid esters, e.g. isopropyl myristate and isopropyl palmitate; polyols or esters thereof, e.g., propylene glycol, ethylene glycol, glycerol,

butanediol, and polyethylene glycol; ethanolamine, diethanolamine, and trietanolamine; terpenes; dimethyl isosorbide; alkanones, and mixtures thereof.

Suitable pH-adjusting agents are selected from the group comprising organic or inorganic acids or bases, e.g., citric acid, acetic acid, fumaric acid, tartaric acid, phosphoric acid and hydrochloric acid, sodium hydroxide, potassium hydroxide, ammonium hydroxide, and triethanolamine. The pH of the topical pharmaceutical composition of the present disclosure is adjusted from about 3 to 11. In some embodiments, the pH is about 3 to about 8, or about 3 to about 6. In some embodiments, the pH is about 3 to about 6.

In some embodiments, the composition comprises a humectant. In some embodiments, suitable humectants can be selected from the group comprising propylene glycol, glycerin, butylene glycol, sorbitol, triacetin and mixtures thereof.

In some embodiments, the composition further comprises one or more additional anti-acne agents, e.g., a second anti-acne agent. These agents include, but are not limited to, benzoyl peroxide, salicylic acid, azelaic acid, antibiotics e.g. clindamycin, erythromycin, retinoids other than isotretinoin, and mixtures thereof.

In some embodiments, the composition does not cause any irritation when applied to the skin. In some embodiments, the composition has a greater than 50%, greater than 80%, greater than 90%, greater than 95% or greater than 99% reduction in irritation when applied to the skin relative to Isotrex.

In some embodiments, the composition, the composition has a firmness of not less than about 10 grams, preferably in the range of about 10 to about 100 grams, about 20 grams to 75 grams, or about 10 grams to 50 grams.

In some embodiments, the composition has a spreadability of more than about 1 cm, preferably in the range of about 1 cm to about 6 cm.

In some embodiments, the composition has a cohesiveness of more than 10 grams, preferably in the range of about 10 to about 200 grams.

In some embodiments, the composition has an index of viscosity less than about -2 grams, preferably in the range of about -2 grams to -100 grams.

In some embodiments, the disclosure provides for a method of treating acne, wherein said method comprises applying topically an effective about of a stable, substantially aqueous composition comprising form about 0.001% to about 1.5% of isotretinoin by total

weight of the composition. In some embodiments, the method of treating acne comprises administering any of the compositions described herein.

In some embodiments, the disclosure provides for a method of treating acne, wherein the composition is applied 1 time to 6 times per day, 1 time to 5 times per day, 1 time to 4 times per day, 1 time to 3 times per day, 1 time to 2 times per time, or 1 time, 2 times, 3 times, or 4 times per day.

In some embodiments, the disclosure provides a kit comprising:

(a) a stable substantially aqueous topical composition of isotretinoin; and

(b) an applicator (or device) for applying the composition.

In some embodiments, the present disclosure provides a process of preparing a stable substantially aqueous topical composition comprising isotretinoin wherein the process comprises:

(a) dissolving preservative, antioxidant and chelating agent in water.

(b) dissolving viscosity-enhancing agent in the solution of step (a) under stirring to form a viscous solution or gel.

(c) dissolving or dispersing isotretinoin and antioxidant in a water miscible solvent

(d) combining (b) & (c) to form the composition, and

(e) adjusting the pH from about 4.5 to about 5.5.

The phrase "substantially aqueous pharmaceutical composition" as used herein means that the composition contains more than 70% w/w of water, or more than 80% w/w of water, or more than 85% w/w of water or more than about 90% w/w of water or more than 95% w/w of water.

Stable substantially aqueous topical composition of isotretinoin may be sprayed or delivered by tube and therefore, formulation may be packed into container suitable for dispensing as solution, suspension, spray or a gel as desired. The formulation, after delivery, will tend to form a film, and the amount of viscosity enhancing agent and other excipients may be adjusted to determine whether the resulting film will be loose or tight, and whether the film may run before setting, or set straight away.

The following examples illustrate the invention but do not limit the scope of invention.

Example 1

Aqueous gel of isotretinoin

Ingredients	Quantity (% w/w)
Isotretinoin	0.10
Diethylene glycol monoethyl ether	15.00
Butylated hydroxy anisole	0.05
Carbopol 980P	1.25
Disodium edetate	0.10
Sodium benzoate	0.20
Ascorbic acid	0.05
Triethanolamine	0.3
Purified water q.s to	100.00

Procedure

1. Sodium benzoate, ascorbic acid and disodium edetate were dissolved in purified water under stirring to get a clear solution.
2. Carbomer 980P was dissolved in the solution of step 1 under stirring to form a viscous gel.
3. Butylated hydroxy anisole and isotretinoin were dissolved in diethylene glycol monoethyl ether under stirring to form a clear solution.
4. Solution of step 3 was added to the gel of step 2 under stirring.
5. Finally, the pH of the gel of step 4 was adjusted to about 5 with triethanolamine.

Example 2

Viscous aqueous solution of isotretinoin

Ingredients	Quantity (% w/w)
Isotretinoin	0.10
Diethylene glycol monoethyl ether	15.00
Butylated hydroxy anisole	0.05
Carbopol 980P	0.40

Disodium edetate	0.10
Sodium benzoate	0.20
Ascorbic acid	0.05
Triethanolamine	0.3
Purified water q.s to	100.00

Procedure

1. Sodium benzoate, ascorbic acid and disodium edetate were dissolved in purified water under stirring to get a clear solution.
2. Carbomer 980P was dissolved in the solution of step 1 under stirring to form a viscous solution.
3. Butylated hydroxy anisole and isotretinoin were dissolved in diethylene glycol monoethyl ether under stirring to form a clear solution.
4. Solution of step 2 was mixed with solution of step 3 under stirring to form a homogenous viscous solution.
5. Finally, the pH of the solution of step 4 was adjusted to about 5 with triethanolamine.

Firmness, Cohesiveness, Index of Viscosity and Spreadibility

Gel and Topical Solution were prepared according to Example 1 and Example 2.

Firmness, cohesiveness, and index of viscosity were calculated by texture Analyser TAXT Plus from Stable Micro Systems, UK. To calculate Firmness, Cohesiveness, Index of Viscosity, 80gm of sample was taken.

To calculate spreadibility, a sample of 0.1 g of each formula was pressed between two glass slides and left for about 5 minutes. When no more spreading was expected diameters of spreaded circles were measured in cm and were taken as comparative values for spreadibility.

Table 1: Firmness, Cohesiveness, Index of Viscosity and Spreadibility of the gel and Solution composition prepared as per Example 1 and Example 2

Physical Parameters	Topical Gel (as per Example 1)	Topical Solution (as per Example 2)
Firmness	46 grams	15 grams
Cohesiveness	131 grams	41 grams
Index of Viscosity	-28 grams	-3.7 grams
Spreadibility	4.9 cm	2.6 cm

Stability Data

The gel prepared according to Example 1 were subjected to stability studies. The compositions were stored at a temperature of 40°C and a relative humidity of 75% RH for a period of three months, and analyzed for isotretinoin contents by HPLC method. The results of the analysis are represented in Table 2.

Table 2: Stability Data of the gel composition prepared as per Example 1

Degradation product **(% w/w)**	**Initial** **75% RH**	**3Month/ 40 °C**
5, 6 Epoxy-13-cis retinoic acid	0.06	0.07
Total Related Substance	0.25	0.29

Aqueous topical pharmaceutical gel composition of isotretinoin was found to be stable.

In-Vitro Release Data

An in-vitro release test was performed using a Franz diffusion cell having an Ultipor N66 membrane (Nylon 6,6; 25mm, 0.2µm). The receptor solution used was ethanol and water (55:45, v/v). 0.01 % w/w isotretinoin gel prepared according to Example 1 was placed uniformly on the membrane at a temperature of 32° C.±1.0° C. The amount of isotretinoin released was determined using an HPLC method and was analyzed using a UV detector at 350 nm. The mean isotretinoin release rate from the gel prepared as per Example 1 is given in Table 3.

Table 3: Mean In-vitro Release Rate of Isotretinoin Gel Prepared as per Example 1

	Mean Release rate ($\mu g/cm^2/h^{1/2}$)
Test	21.08
Control	19.81

In vitro release rates of isotretinoin between development batch (test sample) and control (reference) sample of isotretinoin topical gel (0.1% w/w) were analyzed. The data from Table 3 demonstrates the release rates of isotretinoin from the test sample is comparable with control sample of isotretinoin topical gel (0.1% *w/w).*

Claims:

1. A stable substantially aqueous topical pharmaceutical composition comprising from about 0.001% w/w to about 1.5 % w/w of isotretinoin based on total weight of the composition, wherein the composition comprises degradation products of isotretinoin in an amount of less than 2% w/w based on total weight of the composition when stored at 40°C and 75% RH for a period of at least 3 months.

2. The stable substantially aqueous topical pharmaceutical composition according to claim 1, wherein the composition further comprises 5,6-epoxy-13-cis retinoic acid in an amount of less than about 2 % w/w based on total weight of the composition.

3. The stable substantially aqueous topical pharmaceutical composition according to claim 1, wherein the composition has a viscosity of at least 3000 cps at room temperature (20 °C -25 °C) determined by a Brookfield viscometer.

4. The stable substantially aqueous topical pharmaceutical composition according to claim 1, wherein the composition comprises a viscosity-enhancing agent.

5. The stable substantially aqueous topical pharmaceutical composition according to claim 4, wherein the viscosity-enhancing agent is present in an amount of an amount of about 0.05% to about 20% w/w based on the total weight of the composition.

6. The stable substantially aqueous topical pharmaceutical composition according to 4, wherein the viscosity-enhancing agent is selected from the group consisting of gums e.g. karaya gum, locust bean gum, guar gum, xanthan gum, arabic gum, tragacanth gum, carrageenan, pectin, agar, alginic acid, and sodium alginate; cellulosic derivatives, e.g. hydroxypropyl methyl cellulose, hydroxypropyl cellulose, methylcellulose, hydroxyethyl cellulose, sodium carboxymethylcellulose, microcrystalline cellulose, chitosan, and other synthetic polymers e.g. Carbopol 940, Carbopol 980, Carbopol 974P, Carbopol 971P, Carbopol 934P, methacrylates and polyacrylates, alginic acid-propylene glycol esters, polyoxyethylene-polyoxypropylene copolymers, polyvinyl pyrrolidone, polyethylene glycol, polyethylene oxide, polyvinyl alcohol, silicon dioxide, and mixtures thereof.

7. The stable substantially aqueous topical pharmaceutical composition according to claim 1, wherein the composition further comprises one or more pharmaceutically acceptable excipients selected from the group consisting of a co-solvent, an alkalinizer, an

antioxidant, a chelating agent, a preservative, a surfactants, a penetration enhancer, a pH-adjusting agent, a humectant, a perfume, and mixtures thereof.

8. The stable substantially aqueous topical pharmaceutical composition according to claim 7, wherein the alkalinizer is selected from the group consisting of triethanolamine and sodium hydroxide.

9. The stable substantially aqueous topical pharmaceutical composition according to claim 8, wherein the alkalinizer is present in an amount of at least 0.01 % w/w based on the total weight of the composition.

10. The stable substantially aqueous topical pharmaceutical composition according to claim 1, wherein the composition does not cause any irritation when applied to the skin.

11. The stable substantially aqueous topical pharmaceutical composition according to claim 1, wherein the composition has spreadibility in the range of about 1 cm to 6 cm.

12. The stable substantially aqueous topical pharmaceutical composition according to claim 1, wherein the composition has a firmness of not less than about 10g.

13. The stable substantially aqueous topical pharmaceutical composition according to claim 1, wherein the composition has a cohesiveness of more than about 10g.

14. The stable substantially aqueous topical pharmaceutical composition according to claim 1, wherein the composition has an index of viscosity of less than about -2g.

15. A stable substantially aqueous topical pharmaceutical composition comprising from about 0.001% w/w to about 1.5 % of isotretinoin based on total weight of the composition, wherein the composition has a pH of about 3 to about 11 and comprises degradation products in an amount of less than 2% w/w based on total weight of the composition when stored at 40°C and 75% RH for a period of at least 3 months.

16. A method of treating acne, wherein the method comprises applying topically an effective about of a stable substantially aqueous composition comprising form about 0.001% to about 1.5% of isotretinoin by total weight of the composition.

17. The method of claim 16, comprising the composition of any one of claims 1 to 15.

18. The method of claim 17, wherein the composition is applied 1 time to 6 times per day.

19. The method of claim 17, wherein the composition is applied 1 time to 2 times per day.

20. A process of preparing a stable substantially aqueous topical composition comprising isotretinoin wherein the process comprises:

(a) dissolving preservative, antioxidant and chelating agent in water.

(b) dissolving viscosity-enhancing agent in the solution of (a) under stirring to form a viscous solution or gel.

(c) dissolving or dispersing isotretinoin and antioxidant in a water miscible solvent

(d) combining (b) & (c) to form the composition, and

(e) adjusting the pH from about 4.5 to about 5.5.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB17/56453

A. CLASSIFICATION OF SUBJECT MATTER
IPC - A61K 9/48, 31/202 (2018.01)
CPC - A61K 9/4875, 31/202

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)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
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Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2016/0128962 A1 (SUN PHARMACEUTICAL INDUSTRIES LIMITED) 12 May 2016; paragraphs [0005]-[0006], [0022], [0024], [0038], [0058]; claim 41	1, 3-10, 15-16, 20
Y	US 2016/0038451 A1 (QURETINO THERAPEUTICS, INC.) 11 February 2016; paragraphs [0008], [0130], [0147]-[0148]	1, 3-6
Y	US 2005/0226899 A1 (CASTIGLIONI, M et al.) 13 October 2005; paragraphs [0013]-[0015], [0024]; claims 1, 12, 41	1, 7-10, 16
Y	WO 2013/124820 A1 (RANBAXY LABORATORIES LIMITED) 29 August 2013; page 3, lines 18-22	15, 20
Y	US 2016/0271070 A1 (SUN PHARMACEUTICAL INDUSTRIES LIMITED) 22 September 2016; paragraph [0062]	3
A	US 2013/0012582 A1 (CRIMI, R et al.) 10 January 2013; abstract	2, 11-14

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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"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
19 January 2018 (19.01.2018)	06FEB 2018
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB17/56453

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 17-19
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.