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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 November 2022 (17.11.2022)

WIPO | PCT

(10) International Publication Number
WO 2022/238745 A1

(51) International Patent Classification:
A61K 9/00 (2006.01) *A61P 17/06* (2006.01)
A61K 31/435 (2006.01)

(21) International Application Number:
PCT/IB2021/058243

(22) International Filing Date:
10 September 2021 (10.09.2021)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
202121021777 14 May 2021 (14.05.2021) IN

(71) Applicant: **ZYDUS LIFESCIENCES LIMITED** [IN/IN]; Zydus Corporate Park, Scheme No. 63, Survey No. 536, Khoraj (Gandhinagar), Nr. Vaishnodevi Circle, Sarkhej-Gandhinagar Highway, Ahmedabad-382481, Gujarat (IN).

(72) Inventors: **KANNAN, M. E.**; Zydus Lifesciences Limited, Zydus Corporate Park, Scheme No. 63, Survey No. 536, Khoraj (Gandhinagar), Nr. Vaishnodevi Circle, Sarkhej-Gandhinagar Highway, Ahmedabad-382481, Gujarat (IN). **JAIN, Mukul**; Zydus Lifesciences Limited, Zydus Corporate Park, Scheme No. 63, Survey No. 536, Khoraj (Gandhinagar), Nr. Vaishnodevi Circle, Sarkhej-Gandhinagar Highway, Ahmedabad-382481, Gujarat (IN). **LADDHA, Ritu**; Zydus Lifesciences Limited, Zydus Corporate Park, Scheme No. 63, Survey No. 536, Khoraj (Gandhinagar), Nr. Vaishnodevi Circle, Sarkhej-Gandhinagar Highway, Ahmedabad-382481, Gujarat (IN). **UKAWALA, Mukesh**; Zydus Lifesciences Limited, Zydus Corporate Park, Scheme No. 63, Survey No. 536, Khoraj (Gandhinagar), Nr. Vaishnodevi Circle, Sarkhej-Gandhinagar Highway, Ahmedabad-382481, Gujarat (IN). **PATEL, Jitendra**; Zydus Lifesciences Limited, Zydus Corporate Park, Scheme No. 63, Survey No. 536, Khoraj (Gandhinagar), Nr. Vaishnodevi Circle, Sarkhej-Gandhinagar Highway, Ahmedabad-382481, Gujarat (IN). **SHARMA, Jaymeen**; CZydus Lifesciences Limited, Zydus Corporate Park, Scheme No. 63, Survey No. 536, Khoraj (Gandhinagar), Nr. Vaishnodevi Circle, Sarkhej-Gandhinagar Highway, Ahmedabad-382481, Gujarat (IN).

(74) Agent: **KULSHRESHTHA, Garima** et al.; Subramaniam & Associates, 7th Floor, M3M Cosmopolitan, Sector 66, Golf Course Extension Road, National Capital Region, Gurugram 122001 (IN).

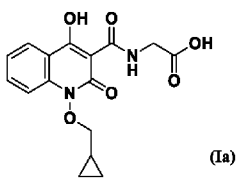
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN, KP, KR, KW, 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, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, 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).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

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

(54) Title: TOPICAL PHARMACEUTICAL COMPOSITION OF HIF PROLYL HYDROXYLASE INHIBITORS



(Ia)

(57) Abstract: Present invention relates to topical pharmaceutical composition of suitable HIF prolyl hydroxylase inhibitors. Preferably, present invention is about the topical pharmaceutical composition of compound of formula (Ia). Disclosed topical pharmaceutical composition comprises compound of formula (Ia) or its pharmaceutically acceptable salts and suitable pharmaceutically acceptable excipients. Such composition is useful for treating skin disorders.

WO 2022/238745 A1

TOPICAL PHARMACEUTICAL COMPOSITION OF HIF PROLYL HYDROXYLASE INHIBITORS

FIELD OF THE INVENTION

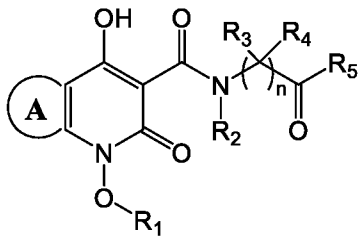
Present invention relates to topical pharmaceutical composition of HIF prolyl hydroxylase inhibitors or pharmaceutically acceptable salts thereof. Specifically, present invention relates to topical pharmaceutical composition of compound of formula (Ia) and pharmaceutically acceptable salts thereof. Invention also relates to process for the preparation of topical pharmaceutical composition of compound of formula (Ia) and pharmaceutically acceptable salts thereof.

BACKGROUND OF THE INVENTION

Hypoxia-inducible factor (HIF) is a heteroduplex, with α and β subunit. The beta subunit is usually present in excess, while the alpha subunit is the limiting factor in the formation of the functional dimer. The HIF-α subunit binds with the β subunit in the nucleus and, with the cooperation of cofactors, binds to DNA sequences called hypoxia response elements, and hence induces expression of target genes. There are three isoforms of the α subunit, HIF-1α, HIF-2α and HIF-3α. The activity of HIF is regulated via hydroxylation at two proline residues by an oxygen-sensitive family of prolyl hydroxylase enzymes (PHD), known as PHD1, PHD2 and PHD3. Hydroxylation at one or both of these proline residues allows binding of HIF-α first by the von Hippel--Lindau tumor suppressor protein (pVHL) and then by ubiquitin ligase which results in rapid ubiquitination and proteosomal degradation. The HIF-α subunits are also regulated by hydroxylation at a C-terminal asparagine residue by factor inhibiting HIF (FIH), an oxygen-dependent hydroxylase enzyme. Factor inhibiting HIF prevents the recruitment of transcriptional coactivators, thereby blocking the activity of HIF.

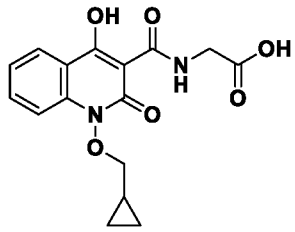
Some of the prolyl hydroxylase inhibitors have been disclosed in EP661269, WO2007070359, WO2008076425, WO2011007856, WO2012106472, and WO2013043621. Specifically WO2004108681 and WO2008002576 covers the prolyl hydroxylase inhibitors named Roxadustat and Vadadustat respectively.

WO2014102818 discloses compounds of the following general formula (I) and US10899713 covers the process for the preparation of these compounds of formula



(I)

These compounds are reported to be useful for the treatment of anemia. It has surprisingly now been found that compound of formula (Ia) as given below:



formula (Ia)

and its pharmaceutically acceptable salts are effective in the treatment of some skin inflammatory related diseases. However, any specific topical pharmaceutical composition has not been developed yet. Hence it is necessary to develop topical pharmaceutical composition.

The merits of topical administration is that it overcomes the problems associated with oral compositions, use of a topical formulation is beneficial as it avoids first-pass metabolism, circumvents gastrointestinal ("GI") absorption, can allow delivery of an active ingredient with a relatively short biological half-life, and/or a narrow therapeutic window and facilitates uniform plasma dosing of the active ingredient. Further, there is an unmet need for improved patient compliant topical formulations that are effective in the treatment of skin disorders, and which provide improved delivery of the active agent at the desired site of action, with decreased side effects if any, increased ease of use for the patient, and longer duration of action.

EMBODIMENTS OF THE INVENTION

In an embodiment, present invention relates to topical pharmaceutical composition of HIF prolyl hydroxylase inhibitors or pharmaceutically acceptable salts thereof.

In another embodiment, present invention relates to a topical pharmaceutical composition comprising HIF prolyl hydroxylase inhibitors or pharmaceutically acceptable salts thereof and one or more suitable pharmaceutically acceptable excipients.

In another embodiment, present invention provides process for the preparation of topical pharmaceutical composition of prolyl hydroxylase inhibitors or pharmaceutically acceptable salts thereof.

In an embodiment, present invention relates to topical pharmaceutical composition of compound of formula (Ia) or its pharmaceutically acceptable salts.

In another embodiment, present invention relates to a topical pharmaceutical composition comprising compound of formula (Ia) or its pharmaceutically acceptable salts and one or more suitable pharmaceutically acceptable excipients. In yet another embodiment, present invention relates to process for the preparation of topical pharmaceutical composition of compound of formula (Ia) or its pharmaceutically acceptable salts.

In an embodiment, the present invention relates to topical pharmaceutical compositions comprising compound of formula (Ia) in the form such as lotion, gel, spray, ointment, cream, foam, paste, suspension and solution.

In another embodiment, the present invention relates to use of topical pharmaceutical composition in skin related disorders.

DESCRIPTION OF THE INVENTION

Definitions:

'Topical formulation' or 'Topical composition' means a formulation or composition in which drug may be placed for the direct application to the application to skin surface, hair, nail or mucosal tissues from which an effective amount of drug is released.

'Treatment' means the managing a medical condition of a subject to cure, ameliorate, stabilize or prevent a disease, disorder or a pathological condition.

'Pharmaceutically acceptable excipient' or 'excipient means pharmacologically inactive substances that are added to the preparation of pharmaceutical composition/formulation in addition to the active pharmaceutical ingredient.

Solubilizers/co-solvents, permeation enhancers, humectant, antioxidants, preservative, chelating agent, acidifying/alkalizing agents, gelling agents, emollient/ stiffening agent, emulsifying agents, ointment bases.

Term '**A**' anywhere in specification denotes Maximum individual unknown degradation product. The amount of **A** should not more than 0.50% by area percentage of HPLC in topical pharmaceutical composition.

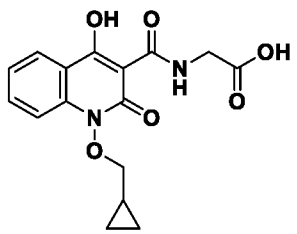
Term '**B**' in stability data denotes total degradation product. The amount of **B** in topical pharmaceutical composition should not more than 2.00% by area percentage of HPLC.

Impurity **D** is the substance (1-(but-3-en-1-yloxy)-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carbonyl)glycine forms in minor amount during the synthesis of compound of formula (Ia). The amount of Impurity **D** in pharmaceutical composition should not be more than 1.00% by area percentage of HPLC.

Present invention relates to topical pharmaceutical composition of HIF prolyl hydroxylase inhibitors or pharmaceutically acceptable salts thereof.

In one of the embodiment, HIF prolyl hydroxylase inhibitors are selected from Roxadustat, Vadadustat, Molidustat and compounds of formula (I) or pharmaceutically acceptable salts thereof.

In one of the preferred embodiment, present invention relates to topical pharmaceutical composition of compound of formula (Ia) or its pharmaceutically acceptable salts.



formula (Ia)

In another embodiment, pharmaceutically acceptable salts of compound of formula (Ia) wherein cations for salt are selected from calcium, sodium, potassium, lithium, barium, strontium, magnesium, cesium, copper, cobalt , iron, manganese, lead, aluminum, cadmium , silver, zinc, ammonium, methylamine, dimethylamine, ethylamine, diethyl amine, n-propyl

amine, isopropyl amine, diisopropyl amine, N-methyl isopropyl amine, n-butyl amine, t-butyl amine, 2-butamine, 1,2-ethane diamine, N-methylglucamine, N,N,N-trimethyl ethanolamine hydroxide (choline), tromethamine, cyclohexylamine, N-methyl cyclohexylamine, guanidine, N-(4-aminobutyl) guanidine, dicyclohexylamine, benzene-methanamine, ethanolamine, diethanolamine, tris-(hydroxymethyl)methylamine, hydroxylamine, methanaminium, benzylamine, N-methylbenzylamine, N-ethyl benzylamine, 4-methoxybenzylamine, pyrrolidine, piperidine, piperazine, morpholine, 2-aminopyrimidine, 2-thiopheneethanamine, (2*S*)-3,3-dimethyl-2-butanamine, cyclopentanamine, cycloheptanamine, meglumine, benethamine, dibenzylamine, diphenylamine, α-naphthylamine, O-phenylenediamine, 1,3-Diaminopropane, (*S*)-α-naphthylethylamine, (*S*)-3-methoxyphenylethylamine, (*S*)-4-methoxyphenylethylamine, (*S*)-4-chlorophenylethylamine, (*S*)-4-methylphenylethylamine, cinchonine, cinchonidine, (-)-quinine, triethanolamine, imidazole, ethylenediamine, epolamine, morpholine 4-(2-hydroxyethyl), N-N-diethylethanolamine, deanol, hydrabamine, betaine, adamantanamine, L-adamantanmethylamine, tritylamine, glucamine, N-methyl pyrrolidine, urea, procaine, metformin, hexane-1,6-diamine, 2-(2-aminoethoxy)ethanamine, N-methylmorpholine, and N-ethylmorpholine, alanine, lysine, arginine, histidine, threonine, proline, glutamine and glycine and the like.

In another embodiment, topical pharmaceutical composition comprising compound of formula (Ia) in therapeutically effective amount selected from 0.01%w/w to 20.00 % w/w. In one of the preferred embodiment topical pharmaceutical composition comprising compound of formula (Ia) in therapeutically effective amount selected from 1.00%w/w to 10.00%w/w. In yet another preferred embodiment, topical pharmaceutical composition comprising compound of formula (Ia) is in amount selected from 1.00%w/w to 5.00%w/w.

In a preferred embodiment, the present invention provides topical pharmaceutical compositions comprising compound of formula (Ia) in the form such as lotion, gel, spray, ointment, cream, foam, paste, suspension, solution and the like.

In another preferred embodiment, present invention provides topical pharmaceutical compositions comprising compound of formula (Ia) or its pharmaceutically acceptable salts and one or more suitable pharmaceutically acceptable excipients.

Suitable pharmaceutically acceptable excipients includes but not limited to Solubilizers/co-solvents, permeation enhancers, humectant, antioxidants, preservative, chelating agent,

acidifying/alkalizing agents, gelling agents, emollient/ stiffening agent, emulsifying agents, ointment bases.

In one of the embodiment, present invention provides topical pharmaceutical composition in gel form comprising compound of formula (Ia) or its pharmaceutically acceptable salts and suitable pharmaceutically acceptable excipients.

Pharmaceutically acceptable excipients for topical gel composition are selected from gelling agent, humectant, chelating agents, permeation enhancers, preservatives, antioxidants, solubilizing agents, acidifying/alkalizing agent and the like. In a preferred embodiment topical gel composition comprising compound of formula (Ia) in therapeutically effective amount selected from 1.00%w/w to 10.00%w/w. In yet another embodiment, gel composition comprising compound of formula (Ia) in therapeutically effective amount of 3.00% w/w. In another embodiment, composition comprising pharmaceutically acceptable excipients gelling agent of about 1.00to 10.00%w/w, solubilizers or co-solvent of about 0.10 to 30.00%w/w, alkalizing agent of about 0.01 to 10.00%w/w and purified water to adjust the sufficient quantity.

In another embodiment, topical gel formulation of 3.00%w/w compound of formula (Ia) further comprising 2.00%w/w hydroxyethyl cellulose, 0.40%w/w sodium hydroxide, 5.00%w/w glycerin and 89.60%w/w purified water to adjust the quantity.

In one of the embodiment, present invention provides topical pharmaceutical composition in solution form comprising compound of formula (Ia) or its pharmaceutically acceptable salts and suitable pharmaceutically acceptable excipients.

Pharmaceutically acceptable excipients for topical solution composition are selected from humectant, chelating agents, permeation enhancers, preservatives, antioxidants, solubilizing agents, acidifying/alkalizing agent and the like.

In another embodiment, topical solution composition comprising compound of formula (Ia) in therapeutically effective amount selected from 0.01%w/w to 10.00 % w/w. In a preferred embodiment topical solution composition comprising compound of formula (Ia) in therapeutically effective amount is 5.00%w/w. In one of the embodiment, topical solution of compound of formula (Ia) further comprising alkalizing agent of about 0.01 to 10.00 %w/w;

solubilizing agents of about 0.10 to 30.00 %w/w and purified water to adjust the total volume accordingly.

In a preferred embodiment, topical solution of 5.00%w/w compound of formula (Ia) comprising 0.62%w/w sodium hydroxide and 5.00%w/w glycerin and 89.38%w/w purified water to adjust the total volume.

In one of the embodiment, present invention provides topical pharmaceutical composition in lotion form comprising compound of formula (Ia) or its pharmaceutically acceptable salts and suitable pharmaceutically acceptable excipients.

Pharmaceutically acceptable excipients for topical lotion composition are selected from gelling agent, humectant, emulsifying agent, emollient, chelating agents, permeation enhancers, preservatives, antioxidants, solubilizing agents, acidifying/alkalizing agent and the like.

In another embodiment, topical lotion composition comprising compound of formula (Ia) in therapeutically effective amount selected from 0.01%w/w to 10.00 % w/w. In a preferred embodiment topical lotion composition comprising compound of formula (Ia) in therapeutically effective amount selected from 3.00%w/w. In one embodiment, topical lotion of compound of formula (Ia) further comprising alkalizing agent of about 0.01 to 10.00 %w/w, solubilizing agents of about 0.10 to 30.00 %w/w, gelling agent of about 0.05 to 1.00%w/w and purified water to adjust the sufficient quantity.

In one preferred embodiment, topical lotion of 3.00%w/w compound of formula (Ia) further comprising 0.75%w/w hydroxyethyl cellulose, 0.40% w/w sodium hydroxide, 5.00% w/w glycerin and 90.85%w/w of purified water to adjust the quantity.

In one of the embodiment, present invention provides topical pharmaceutical composition in cream form comprising compound of formula (Ia) or its pharmaceutically acceptable salts and suitable pharmaceutically acceptable excipients.

Pharmaceutically acceptable excipients for topical cream composition are selected from humectant, emulsifying agent, emollient, chelating agents, permeation enhancers, preservatives, antioxidants, solubilizing agents, acidifying/alkalizing agent and the like.

In another embodiment, topical cream composition comprising compound of formula (Ia) in therapeutically effective amount selected from 0.01%w/w to 10.00 % w/w. In a preferred embodiment topical cream composition comprising compound of formula (Ia) in therapeutically effective amount selected from 1.00%w/w to 5.00%w/w. In another embodiment topical cream composition comprising humectant of about 0.50 to 35.00%w/w, emollient/stiffening agent of about 1.00 to 40.00%w/w, emulsifying agent of about 1.00 to 30.00%w/w, penetration enhancer of about 0.50 to 15.00%w/w, preservatives of about 0.001 to 1.00%w/w, alkalizing agent of about 0.01 to 10.00%w/w and purified water to adjust the quantity.

In a preferred embodiment topical cream composition of 1.00 % w/w compound of formula (Ia) comprises 0.14% w/w sodium hydroxide, 5.00%w/w propylene glycol, 10.00%w/w white soft paraffin, 6.00%w/w liquid paraffin, 7.20%w/w Cetostearyl alcohol, 1.80%w/w Cetomacrogol 1000, 0.05% w/w propyl paraben, 0.10%w/w methyl paraben and 68.71%w/w purified water to adjust the quantity.

In another preferred embodiment topical cream composition of 3.00 % w/w compound of formula (Ia) comprises 0.40% w/w sodium hydroxide, 5.00%w/w propylene glycol, 10.00%w/w white soft paraffin, 6.00%w/w liquid paraffin, 7.20%w/w Cetostearyl alcohol, 1.80%w/w Cetomacrogol 1000, 0.05% w/w propyl paraben, 0.10%w/w methyl paraben and 66.45%w/w purified water to adjust the quantity.

In another preferred embodiment topical cream composition of 5.00 % w/w compound of formula (Ia) comprises 0.62% w/w sodium hydroxide, 5.00%w/w propylene glycol, 10.00%w/w white soft paraffin, 6.00%w/w liquid paraffin, 7.20%w/w Cetostearyl alcohol, 1.80%w/w Cetomacrogol 1000, 0.05% w/w propyl paraben, 0.10%w/w methyl paraben and 64.23%w/w purified water to adjust the quantity.

In one of the embodiment, present invention provides topical pharmaceutical composition in ointment form comprising compound of formula (Ia) or its pharmaceutically acceptable salts and suitable pharmaceutically acceptable excipients.

Pharmaceutically acceptable excipients for topical ointment composition are selected from ointment bases, preservatives, solubilizing agents, emollient, emulsifying agent, permeation enhancers, antioxidants and the like.

In another embodiment, topical ointment composition comprising compound of formula (Ia) in therapeutically effective amount selected from 0.01%w/w to 10.00 % w/w. In one of the preferred embodiment topical ointment composition comprising compound of formula (Ia) in therapeutically effective amount is 1.00 %w/w. In another embodiment topical ointment composition further comprises ointment base of about 2.00 to 99.00%w/w.

In a preferred embodiment, topical ointment composition of 1.00%w/w compound of formula (Ia) further comprises 79.00%w/w polyethylene glycol 400 and 20.00%w/w polyethylene glycol 6000.

In one of the embodiment, present invention provides topical pharmaceutical composition in foam form comprising compound of formula (Ia) or its pharmaceutically acceptable salts and suitable pharmaceutically acceptable excipients.

Pharmaceutically acceptable excipients for topical foam composition are selected from surfactant/ emulsifying agents, propellants, alkalizing agents, solubilizers/ co-solvents emollient / stiffening agents, ointment base and the like.

In another embodiment, topical foam composition comprising compound of formula (Ia) in therapeutically effective amount selected from 0.01%w/w to 10.00 % w/w. In another embodiment, topical foam of compound of formula (Ia) further comprises emollient or stiffening agents of about 0.20 to 10.00%w/w, propellants of about 1.00 to 25.00%w/w, emulsifying agent of about 0.10 to 20.00%w/w, ointment base of about 1.00 to 30.00%w/w, alkalizing agent of about 0.01 to 10.00%w/w, solvents and co-solvents of about 5.00 to 80.00%w/w and purified water to adjust the quantity.

In another embodiment, process for preparation of topical foam comprising following steps:

i. Compound of formula (Ia) is dispersed in a part of Purified water under stirring.
ii. Alkalizing agent is dissolved in another portion of Purified water under stirring.
iii. Solution of Step (ii) is added to mixture of step (i) under stirring. Stirring is continued till clear solution is obtained.
iv. Ointment base, co-solvent and emulsifying agents and remaining amount of purified water are added to solution of step (iii) and mixed under stirring.
v. Solution of Step (iv) is heated to 70°C and maintained at same temperature.

vi. Emollients are mixed, heated and melted to 70°C and maintained at same temperature.

vii. Solution of Step (vi) is added to aqueous solution of step (v) under stirring at 70°C and mixed for 10 min.

viii. The resultant emulsion is cooled to 25-30°C and required amount of solvent is added into it under stirring.

ix. The final mixture is filled in canister with crimp valve.

x. Propellant is filled in to the canister under pressure and sealed.

In one of the embodiment, present invention provides topical pharmaceutical composition in suspension form comprising compound of formula (Ia) or its pharmaceutically acceptable salts and suitable pharmaceutically acceptable excipients.

Pharmaceutically acceptable excipients for topical suspension composition are selected from solubilizing agents/ co-solvent, gelling agents and the like.

In another embodiment, topical suspension composition comprising compound of formula (Ia) in therapeutically effective amount selected from 0.01%w/w to 10.00%w/w. In another embodiment, topical suspension of compound of formula (Ia) further comprises solubilizing agents /co-solvents of about 0.10 to 10.00%w/w, gelling agents of about 0.01 to 10.00%w/w and purified water to adjust the quantity.

In yet another embodiment, process for preparation of topical suspension comprising following steps:

i. Solubilizing agent and gelling agent are dissolved into purified water under stirring. The stirring is continued till clear solution is obtained.

ii. Compound of formula (Ia) is taken in a mortar and approximately 10% percent of suspending vehicle from step I is added to it. This mixture is triturated for 5 minutes continuously.

iii. The resultant suspension is completely transferred into a calibrated measuring cylinder and required volume is made up with remaining vehicle from step I.

iv. The resultant suspension is mixed for approximately 10 minutes.

In one of the embodiment, present invention provides topical pharmaceutical composition in paste form comprising compound of formula (Ia) or its pharmaceutically acceptable salts and suitable pharmaceutically acceptable excipients.

Pharmaceutically acceptable excipients for topical paste composition are selected from gelling agents, ointment bases and the like.

In another embodiment, topical paste composition comprising compound of formula (Ia) in therapeutically effective amount selected form 0.01%w/w to 10.00%w/w. In another embodiment, topical paste comprising gelling agent of about 20.00 to 80.00%w/w and ointment base of about 1.00 to 30.00%w/w.

In yet another embodiment, process for the preparation of topical paste comprising following steps:

i. Various Ointment bases are mixed under stirring as required.
ii. Compound of formula (Ia) is added to above mixture under stirring and mixed for 10 minutes.
iii. The mixture from step (ii) is added to gelling agent gradually in small amounts and triturated.
iv. When addition is completed, the trituration is continued for 15 minutes.

Solubilizers/co-solvents used anywhere in the description may be selected from Dimethyl malonate, diethyl succinate, diethyl glutarate, diethyl adipate, dipropyl adipate, dibutyl sebacate, diisopropyl sebacate, diethyl pimelate, diethyl suberate, diethyl azelate, dibutyl adipate, dibutyl sebacate, methyl ethyl succinate, diethyl ethyl-isopropylmalonate, diethyl isosuccinate, benzyl alcohol, benzyl benzoate, cyclodextrin, glycerine monostearate, lecithin, butylene glycol, dibutyl phthalate, diethyl phthalate, dimethyl ether, diethyl ether, ethyl acetate, ethyl lactate, ethyl oleate, glycofurol, isopropyl alcohol, triacetin, triethanolamine, hexylene glycol, dimethyl sulfoxide (DMSO) and/or dimethyl isosorbide, propylene glycol, glycerin, Diethylene glycol monoethyl ether, dimethyl acetamide, polyethylene glycol, polysorbate 80, 60 & 20, purified water, ethanol and suitable mixture thereof.

Permeation enhancers used anywhere in the description may be selected from polyethylene glycol, polyethylene glycol monolaurate, butanediol, dimethylsulfoxide, decylmethylsulfoxide, diethylene glycol monoethyl ether (e.g., Transcutol® P), Cetomacrogol

1000, lauric acid, oleic acid, valeric acid, isopropyl myristate, isopropyl palmitate, methyl propionate, and ethyl oleate; urea, dimethyl acetamide, dimethylformamide 2- pyrrolidone, ethanolamine, methyl-2 -pyrrolidone, diethanolamine, triethanolamine, terpenes, alkanones, salicylic acid, citric acid, succinic acid and suitable mixtures thereof.

Humectants used anywhere in the description may be selected from glycerin, propylene glycol, dipropylene glycol, polypropylene glycol, urea, polyglycerine, 1,3-butylene glycol, pantothenol, gluconic acid salts, butane diols, Polyethylene glycol and its derivatives, xylitol sorbitol solution, 1,2,6 –hexanetriol and suitable mixtures thereof.

Antioxidants used anywhere in the description may be selected from ascorbic acid (vitamin C), glutathione, lipoic acid, uric acid, carotenes, a-tocopherol (vitamin E), ubiquinol, butylated hydroxyanisole, butylated hydroxytoluene, sodium benzoate, sodium thiosulphate, sodium metabisulphite, propyl gallate (PG, E310), and tertiary-butylhydroquinone, Idebenone, Lycopene and suitable mixtures thereof.

Preservatives used anywhere in the description may be selected from Methyl paraben, Propyl paraben, benzoic acid, imidurea, sorbic acid, potassium sorbate, benzalkonium chloride, phenyl mercuric acetate, chlorobutanol, phenoxyethanol, benzyl alcohol, chlorocresol, metacresol, cetrimonium chloride, benzethonium chloride, sodium edetate, boric acid, phenol and suitable mixtures thereof.

Chelating agents used anywhere in the description may be selected from EDTA, disodium EDTA, trisodium EDTA, EGTA, disodium EGTA, trisodium EGTA, citric acid, phosphoric acid, succinic acid, and suitable mixtures thereof.

Alkalizing agents used anywhere in the description may be selected from trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, meglumine, dicyclohexylamine, N,N'- dibenzylethylenediamine, arginine, lysine, ornithine, sodium bicarbonates, sodium hydroxide, potassium hydroxide and suitable mixtures thereof.

Buffers used anywhere in the description may be selected from citrate/citric acid buffers, acetate/acetic acid buffers, phosphate/phosphoric acid buffers, formate/formic acid buffers, propionate/propionic acid buffers, carbonate/carbonic acid buffers, ammonium/ammonia buffers and suitable mixtures thereof.

Gelling agents used anywhere in the description may be selected from carbomer, Methyl cellulose, sodium carboxy methyl cellulose, Carrageenan, colloidal silicon dioxide, Guar gum, hydroxyethyl cellulose, hydroxypropyl methyl cellulose, hydroxy propyl cellulose, Gelatin, polyethyene oxide, alginic acid, sodium alginate, fumed silica, polyvinylpyrrolidone, polyvinyl alcohol and suitable mixtures thereof.

Emollient/ stiffening agents used anywhere in the description may be selected from carnauba wax, cetyl alcohol, cetyl ester wax, hydrous lanolin, lanolin, lanolin alcohols, paraffin, white soft paraffin, petrolatum. polyethylene glycol, stearic acid, stearyl alcohol, white wax, yellow wax, liquid paraffin, liquid petrolatum, jojoba oil, sesame oil, rapeseed oil, purcellin oil, 2-ethylhexyl palmitate, 2-octyldodecyl stearate, 2-octyldodecyl erucate, isostearyl isostearate, 2-octyldodecyl benzoate, triglycerides of caprylic/capric acids, octyldodecanol, isohexadecane, capmul MCM and suitable mixtures thereof.

Emulsifying agents used anywhere in the description may be selected from polysorbate 20, polysorbate 60, polysorbate 80, poloxamer, Cetostearyl alcohol, Polyoxyethylene lauryl alcohol emulsifying wax, sorbitan monostearate, sorbitan monooleate, sodium lauryl sulphate, propylene glycol monostearate, glyceryl monostearate and suitable mixtures thereof.

Ointment bases used anywhere in the description may be selected from oleaginous bases such as petrolatum, white/yellow petrolatum, liquid paraffin, hard paraffin, white ointment; absorption bases such as lanolin, anhydrous lanolin, cold cream, etc.; water removable bases: hydrophilic ointments, vanishing creams and water; water soluble bases such as polyethylene glycol 200, 300, 400, 1500, 3000, 6000 and suitable mixtures thereof.

Propellants used anywhere in the description may be selected from chlorofluorocarbons and flurocarbons such as chlorodifluoromethane chlorotrifluoromethane, dichlorodifluoromethane, trichlorofluoromethane, tetrafluoroethane, 1,2-dichlorotetrafluoroethane, trichlorofluoroethane, chloropentafluoropropane, chloroheptafluoropropane, heptafluoropropane, perfluorocyclopropane, perfluoropropane, perfluoro-n-butane, perfluoroisobutane, perfluorocyclobutane, perfluorodimethyl ether, perfluorodiethyl ether, perfluorofuran, perfluoromethylamine, bis-(trifluoromethyl)sulfide, and trifluoromethylpentafluorosulfide, alkanes such as methane, n-butane, isobutane, propane, pentane, ethers such as dimethyl ether and suitable mixtures thereof.

Suspending agents used anywhere in the description may be selected from acacia, agar, Alginic acid, bentonite, calcium stearate, carbomer, carboxymethyl cellulose, carrageenan, methyl cellulose, powder cellulose, ceratonia, colloidal silicon dioxide, dextrin, gelatin, guar gum, hectorite, hypromellose, hydroxy propyl cellulose, magnesium silicate, kaolin, maltitol, polycarbophil, polyethylene glycol, potassium alginate, povidone, propylene glycol alginate, saponite, sodium starch glycolate, sucrose, tragacanth, xanthan gum and suitable mixture thereof.

In another embodiment, topical pharmaceutical composition comprising compound of formula (Ia) in therapeutically effective amount selected from 0.01%w/w to 20.00 % w/w. In a preferred embodiment topical pharmaceutical composition comprising compound of formula (Ia) in therapeutically effective amount selected from 1.00%w/w to 10.00%w/w.

In another embodiment, topical pharmaceutical composition comprising compound of formula (Ia) wherein relative amount of maximum individual unknown degradation product **A** to compound of formula (Ia), should not more than 0.50% by area percentage of HPLC. In another embodiment, relative amount of total degradation product **B** to compound of formula (Ia), should not more than 2.00% by area percentage of HPLC in topical pharmaceutical composition. In another embodiment, relative amount of impurity **D** to compound of formula (Ia), should not more than 1.00% by area percentage of HPLC.

In another embodiment, pH of the topical pharmaceutical composition is selected from the range of 4.0 to 9.0. In a preferred embodiment, pH range of topical pharmaceutical composition comprising compound of formula (Ia) is selected from 6.0 to 8.5.

In another embodiment, present invention provides process for the preparation of topical pharmaceutical composition of compound of formula (Ia) or its pharmaceutically acceptable salts as provided in following examples.

In yet another embodiment present invention relates to use in treatment of skin related disorders. In another embodiment topical pharmaceutical composition of compound of formula (Ia) is useful in treating psoriasis.

The skin related diseases include: dermatomycosis, scleroderma, epidermolysis bullosa, eczema and systemic lupus erythematous affecting skin. Some other skin diseases such as hives, acneiform eruptions, autoinflammatory diseases (Blau syndrome, Majeed syndrome,

Muckle–Wells syndrome), chronic blistering diseases, skin mucus diseases, inflammation of skin appendages, diseases of alteration in pigmentation, drug-induced skin diseases, eosinophilic cutaneous conditions, bacterial or viral or fungal or parasite skin infections, lichen planus, lymphoid-related cutaneous conditions, monocyte-and macrophage-related cutaneous inflammation, reactive neutrophilic cutaneous condition, utricaria and other skin inflammation of unknown origin could also treated using topical pharmaceutical composition of compound of formula (Ia).

Examples

The invention now being generally described, will be more readily understood by reference to the following examples, which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and are not intended to limit the invention.

The following Examples illustrate the invention. All temperatures are in degrees Centigrade (r.t.=room temperature):

Example 1: Topical Solution of compound of formula (Ia)

Sr. No.	**Ingredients**	**% w/w**
1	Compound of formula (Ia)	5.00
2	Sodium hydroxide	0.62
3	Glycerin	5.00
4	Purified water	89.38
	Total	100.00

A pharmaceutically acceptable solution is obtained from the above ingredients, when the preparation process is carried out in the following steps:

I. Compound of formula (Ia) is dispersed in a part of Purified water under stirring.

II. Sodium hydroxide is dissolved in a part of Purified water under stirring.

III. Solution from Step II is added to mixture of step I under stirring. Stirring is continued till clear solution is obtained.

IV. Glycerin is added to solution of step III and mixed under stirring.

V. Total weight of the formulation is adjusted to required weight with remaining portion of Purified water.

Stability study of Example 1

Sr. No	Test	Initial	40°C ± 2°C / 75% RH ± 5 %RH		25°C ± 2°C / 60% RH ± 5 %RH
			1 month	3 month	3 month
1	pH	8.0	7.5	7.5	7.5
2	Assay (%)	99.1	99.7	101.7	104.7
3	Related substances				
	Impurity D (%)	0.11	0.10	0.09	0.10
	A (%)	0.06	0.08	0.08	0.09
	B (%)	0.21	0.23	0.18	0.20

Example 2: Topical gel of Compound of formula (Ia)

Sr. No.	Ingredients	% w/w
1	Compound of formula (Ia)	3.00
2	Sodium hydroxide	0.40

3	Glycerin	5.00
4	Hydroxyethyl cellulose	2.00
5	Purified water	89.60
	Total	100.00

A pharmaceutically acceptable gel is obtained from the above ingredients, when the preparation process is carried out in the following steps:

I. Compound of formula (Ia) is dispersed in a part of Purified water under stirring.

II. Sodium hydroxide is dissolved in remaining portion of Purified water under stirring.

III. Solution of Step II is added to mixture of step I under stirring. Stirring is continued till clear solution is obtained.

IV. Glycerin is added to solution of step III and mixed under stirring.

V. Hydroxyethyl cellulose is slowly added to solution of step IV under constant stirring and mixed till clear homogenous gel is obtained.

Stability study of Example 2

Sr. No	**Test**	**Initial**	**40°C ± 2°C / 75% RH ± 5 %RH**		**25°C ± 2°C / 60% RH ± 5 %RH**
			1 month	**3 month**	**3 month**
1	pH	7.5	7.5	7.5	7.5
2	Assay (%)	108.0	107.1	107.6	108.9

3	Related substances				
	Impurity D (%)	0.09	0.11	0.11	0.10
	A (%)	0.06	0.08	0.09	0.09
	B (%)	0.20	0.23	0.20	0.19

Example 3: Topical lotion Compound of formula (Ia)

Sr. No.	**Ingredients**	**% w/w**
1	Compound of formula (Ia)	3.00
2	Sodium hydroxide	0.40
3	Glycerin	5.00
4	Hydroxyethyl cellulose	0.75
5	Purified water	90.85
	Total	100.00

A pharmaceutically acceptable lotion is obtained from the above ingredients, when the preparation process is carried out in the following steps:

I. Compound of formula (Ia) is dispersed in a part of Purified water under stirring.

II. Sodium hydroxide is dissolved in remaining portion of Purified water under stirring.

III. Solution of Step II is added to mixture of step I under stirring. Stirring is continued till clear solution is obtained.

IV. Glycerin is added to solution of step III and mixed under stirring.

V. Hydroxyethyl cellulose is slowly added to solution of step IV under constant stirring and mixed till clear homogenous lotion is obtained.

Stability study of Example 3

Sr. No	Test	Initial	40°C ± 2°C / 75% RH ± 5 %RH		25°C ± 2°C / 60% RH ± 5 %RH
			1 month	3 month	3 month
1	pH	8.0	7.5	7.4	7.6
2	Assay (%)	100.5	101.1	101.6	101.1
3	Related substances				
	Impurity D (%)	0.10	0.10	0.08	0.11
	A (%)	0.05	0.09	0.09	0.09
	B (%)	0.19	0.23	0.16	0.21

Example 4(i): Topical cream of Compound of formula (Ia)

Sr. No.	Ingredients	% w/w
1	Compound of formula (Ia)	1.00
2	Propylene glycol	5.00
3	White soft paraffin	10.00
4	Liquid paraffin	6.00

5	Cetostearyl alcohol	7.20
6	Cetomacrogol 1000	1.80
7	Propyl paraben	0.05
8	Methyl paraben	0.10
9	Sodium hydroxide	0.14
10	Purified water	68.71
	Total	100.00

Example 4(ii): Topical cream of Compound of formula (Ia) (3.00% w/w)

Sr. No.	**Ingredients**	**% w/w**
1	Compound of formula (Ia)	3.00
2	Propylene glycol	5.00
3	White soft paraffin	10.00
4	Liquid paraffin	6.00
5	Cetostearyl alcohol	7.20
6	Cetomacrogol 1000	1.80
7	Propyl paraben	0.05

8	Methyl paraben	0.10
9	Sodium hydroxide	0.40
10	Purified water	66.45
	Total	100.00

Example 4(iii): Topical cream of Compound of formula (Ia) (5.00% w/w)

Sr. No.	**Ingredients**	**% w/w**
1	Compound of formula (Ia)	5.00
2	Propylene glycol	5.00
3	White soft paraffin	10.00
4	Liquid paraffin	6.00
5	Cetostearyl alcohol	7.20
6	Cetomacrogol 1000	1.80
7	Propyl paraben	0.05
8	Methyl paraben	0.10
9	Sodium hydroxide	0.62
10	Purified water	64.23

	Total	100.00

A pharmaceutically acceptable cream is obtained from the above ingredients, when the preparation process is carried out in the following steps:

I. Compound of formula (Ia) is dispersed in a part of Purified water under stirring.

II. Sodium hydroxide is dissolved in remaining portion of Purified water under stirring.

III. Solution of Step II is added to mixture of step I under stirring. Stirring is continued till clear solution is obtained.

IV. Propylene glycol is added to solution of step III and mixed under stirring.

V. Solution of Step IV is heated to 70°C and maintained at same temperature.

VI. White soft paraffin, Liquid paraffin, Cetostearyl alcohol and Cetomacrogol 1000 were mixed, heated and melted to 70°C and maintained at same temperature.

VII. Methyl paraben and Propyl paraben are added to solution of step VI and stirred till completely dissolved.

VIII. Solution of Step VII added to aqueous solution of step V under stirring at 70°C and mixed for 10 min.

IX. Mixture of Step VIII is cooled to room temperature along with constant stirring.

Stability study of Example 4 (i) (1% w/w)

Sr. No	**Test**	**Initial**	**40°C ± 2°C / 75% RH ± 5 %RH**		**25°C ± 2°C / 60% RH ± 5 %RH**
			1 month	**3 month**	**3 month**
1	pH	7.2	7.2	7.1	7.1
2	Assay (%)	105.6	106.5	109.3	106.9
3	Related substances				

	Impurity D (%)	0.11	0.10	0.12	0.11
	A (%)	0.06	0.07	0.11	0.10
	B (%)	0.21	0.22	0.28	0.25

Stability study of Example 4 (iii) (3.00% w/w)

Sr. No	**Test**	**Initial**	**40°C ± 2°C / 75% RH ± 5 %RH**		**25°C ± 2°C / 60% RH ± 5 %RH**
			1 month	**3 month**	**3 month**
1	pH	7.4	7.3	7.3	7.4
2	Assay (%)	102.0	102.5	103.1	104.4
3	Related substances				
	Impurity D (%)	0.10	0.10	0.11	0.10
	A (%)	0.05	0.07	0.10	0.08
	B (%)	0.20	0.22	0.26	0.18

Stability studies provided along with above examples shows all prepared examples are stable at 25°C and 40°C for three months. All above formulations may be useful for clinical studies as well as for the treatment of skin related disorders such as psoriasis.

Example 5: Topical ointment of Compound of formula (Ia)

Sr. No.	**Ingredients**	**% w/w**

1	Compound of formula (Ia)	1.00
2	Polyethylene glycol 400	79.00
3	Polyethylene glycol 6000	20.00
	Total	100.00

A pharmaceutically acceptable ointment is obtained from the above ingredients, when the preparation process is carried out in the following steps:

I. Polyethylene glycol 400 is heated at 75°C and maintained at same temperature.

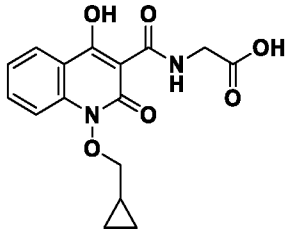
II. Compound of formula (Ia) is dissolved in step I under stirring.

III. Polyethylene glycol 6000 is melted at 75°C and added to solution from solution of Step II under constant stirring at 75°C.

IV. The mixture is then cooled to room temperature along with constant stirring.

We Claim:

1. Topical pharmaceutical composition comprising compound of formula (Ia) and pharmaceutically acceptable excipients wherein compound of formula (Ia) is



formula (Ia)

2. The composition as claimed in claim 1, wherein pharmaceutically acceptable excipients are selected from gelling agents, humectants, chelating agents, permeation enhancers, preservatives, antioxidants, solubilizing agents/ solubilizers / co-solvents, alkalizing agents, emollient/ stiffening agent, emulsifying agent, ointment bases.
3. The composition as claimed in claim 1, wherein therapeutically effective amount of compound of formula (Ia) is selected from 0.01%w/w to 20.00 % w/w, preferably selected from 1.00%w/w to 10.00%w/w.
4. The composition as claimed in claim 1, wherein topical formulation is in the form of lotion, gel, spray, ointment, cream, foam, paste, suspension and solution.
5. The composition as claimed in claim 1 wherein gelling agents are selected from carbomer, methyl cellulose, sodium carboxy methyl cellulose, carrageenan, colloidal silicon dioxide, guar gum, hydroxypropyl methyl cellulose, hydroxyethyl cellulose, hydroxy propyl cellulose, gelatin, polyethyene oxide, alginic acid, sodium alginate, fumed silica, polyvinylpyrrolidone, polyvinyl alcohol and suitable mixtures thereof.
6. The composition as claimed in claim 1 wherein humectants are selected from glycerin, propylene glycol, dipropylene glycol, polypropylene glycol, urea, polyglycerine, 1,3-butylene glycol, pantothenol, gluconic acid salts, butane diols, Polyethylene glycol and its derivatives, xylitol sorbitol solution, 1,2,6 –hexanetriol and suitable mixtures thereof.
7. The composition as claimed in claim 1 wherein chelating agents are selected from EDTA, disodium EDTA, trisodium EDTA, EGTA, disodium EGTA, trisodium EGTA, citric acid, phosphoric acid, succinic acid, and suitable mixtures thereof.
8. The composition as claimed in claim 1 wherein permeation enhancers are selected from polyethylene glycol, polyethylene glycol monolaurate, butanediol,

dimethylsulfoxide, decylmethylsulfoxide, diethylene glycol monoethyl ether (e.g., Transcutol® P), Cetomacrogol 1000, lauric acid, oleic acid, valeric acid, isopropyl myristate, isopropyl palmitate, methyl propionate, and ethyl oleate; urea, dimethyl acetamide, dimethylformamide 2- pyrrolidone, ethanolamine, methyl-2 -pyrrolidone, diethanolamine, triethanolamine, terpenes, alkanones, salicylic acid, citric acid, succinic acid and suitable mixtures thereof.

9. The composition as claimed in claim 1 wherein preservatives are selected from methyl paraben, propyl paraben, benzoic acid, imidurea, sorbic acid, potassium sorbate, benzalkonium chloride, phenyl mercuric acetate, chlorobutanol, phenoxyethanol, benzyl alcohol, chlorocresol, metacresol, cetrimonium chloride, benzethonium chloride, sodium edetate, boric acid, phenol and suitable mixtures thereof.
10. The composition as claimed in claim 1 wherein antioxidants are selected from ascorbic acid (vitamin C), glutathione, lipoic acid, uric acid, carotenes, a-tocopherol (vitamin E), ubiquinol, butylated hydroxyanisole, butylated hydroxytoluene, sodium benzoate, sodium thiosulphate, sodium metabisulphite, propyl gallate (PG, E310), and tertiary-butylhydroquinone, Idebenone, Lycopene and suitable mixtures thereof.
11. The composition as claimed in claim 1 wherein solubilizing agents/ solubilizers / co-solvents are selected from dimethyl malonate, diethyl succinate, diethyl glutarate, diethyl adipate, dipropyl adipate, dibutyl sebacate, diisopropyl sebacate, diethyl pimelate, diethyl suberate, diethyl azelate, dibutyl adipate, dibutyl sebacate, methyl ethyl succinate, diethyl ethyl-isopropylmalonate, diethyl isosuccinate, benzyl alcohol, benzyl benzoate, cyclodextrin, glycerine monostearate, lecithin, butylene glycol, dibutyl phthalate, diethyl phthalate, dimethyl ether, diethyl ether, ethyl acetate, ethyl lactate, ethyl oleate, glycofurol, isopropyl alcohol, triacetin, triethanolamine, hexylene glycol, dimethyl sulfoxide (DMSO) and/or dimethyl isosorbide, propylene glycol, glycerin, Diethylene glycol monoethyl ether, dimethyl acetamide, polyethylene glycol, polysorbate 80, 60 & 20, purified water, ethanol and suitable mixture thereof.
12. The composition as claimed in claim 1 wherein alkalizing agents are selected from trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, meglumine, dicyclohexylamine, N,N'- dibenzylethylenediamine, arginine, lysine, ornithine, sodium bicarbonates, sodium hydroxide, potassium hydroxide and suitable mixtures thereof and buffers are selected from citrate/citric acid buffers, acetate/acetic acid buffers, phosphate/phosphoric acid buffers,

formate/formic acid buffers, propionate/propionic acid buffers, carbonate/carbonic acid buffers, ammonium/ammonia buffers and suitable mixtures thereof.

13. The composition as claimed in claim 1 wherein emollient/ stiffening agent are selected from carnauba wax, cetyl alcohol, cetyl ester wax, hydrous lanolin, lanolin, lanolin alcohols, paraffin, white paraffin, petrolatum, polyethylene glycol, stearic acid, stearyl alcohol, white wax, yellow wax, liquid paraffin, liquid petrolatum, jojoba oil, sesame oil, rapeseed oil, purcellin oil, 2-ethylhexyl palmitate, 2-octyldodecyl stearate, 2-octyldodecyl erucate, isostearyl isostearate, 2-octyldodecyl benzoate, triglycerides of caprylic/capric acids, octyldodecanol, isohexadecane, capmul MCM and suitable mixtures thereof.
14. The composition as claimed in claim 1 wherein emulsifying agent are selected from polysorbate 20, polysorbate 60, polysorbate 80, poloxamer, Cetostearyl alcohol emulsifying wax, sorbitan monostearate, sorbitan monooleate, sodium lauryl sulphate, propylene glycol monostearate, glyceryl monostearate and suitable mixtures thereof.
15. The composition as claimed in claim 1 wherein ointment bases are selected from oleaginous bases such as petrolatum, white/yellow petrolatum, liquid paraffin, hard paraffin, white ointment; absorption bases such as lanolin, anhydrous lanolin, cold cream, etc.; water removable bases: hydrophilic ointments, vanishing creams and water; water soluble bases such as polyethylene glycol 200, 300, 400, 1500, 3000, 6000 and suitable mixtures thereof.
16. Topical pharmaceutical composition comprising compound of formula (Ia) and pharmaceutically acceptable excipients wherein composition is selected from solution, gel, lotion, cream and ointment form.
17. The composition as claimed in claim 16, wherein composition is in gel form comprising compound of formula (Ia) of about 1.00 to 5.00%w/w, gelling agent of about 1.00 to 10.00%w/w, solubilizers or co-solvent of about 0.10 to 30.00%w/w, alkalizing agent of about 0.01 to 10.00%w/w and purified water.
18. The composition as claimed in claim 16, wherein composition is in solution form comprising compound of formula (Ia) of about 1.00 to 5.00%w/w, alkalizing agent of about 0.01 to 10.0%w/w, solubilizing agent of about 0.10 to 30.00% w/w and purified water.
19. The composition as claimed in claim 16, wherein composition is in lotion form comprising compound of formula (Ia) of about 1.00 to 5.00%w/w, gelling agent of

about 0.05 to 1.00%w/w, solubilizers or co-solvent of about 0.10 to 30.00%w/w, alkalizing agent of about 0.01 to 10.00%w/w and purified water.

20. The composition as claimed in claim 16 wherein composition is in cream form comprising 1.00 to 5.00%w/w compound of formula (Ia) and humectant of about 0.50 to 35.00%w/w, emollient/stiffening agent of about 1.00 to 40.00%w/w, emulsifying agent of about 1.00 to 30.00%w/w, penetration enhancer of about 0.50 to 15.00%w/w, preservatives of about 0.001 to 1.00%w/w, alkalizing agent of about 0.01 to 10.00%w/w and purified water to adjust the quantity.
21. The composition as claimed in claim 16 wherein composition is in ointment form comprising about 1.00 to 5.00%w/w compound of formula (Ia) and ointment base of about 2.00 to 99.00%w/w.
22. The composition as claimed in any of above claims is useful for the topical treatment of skin related diseases such as psoriasis.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2021/058243

A. CLASSIFICATION OF SUBJECT MATTER
A61K9/00,A61K31/435,A61P17/06 Version=2021.01

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)

PatSeer, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2014102818 A1 (CADILA HEALTHCARE LIMITED [IN]) 3 July 2014 Examples 2,56, 53, 50, 45, 71; Page 5 lines 2-5 and 21-22; and Claims 9-12	1
Y	Examples 2,56, 53, 50, 45, 71; Page 5 lines 2-5 and 21-22; and Claims 9-12	2-22
Y	US 8598210 B2 (AKEBIA THERAPEUTICS INC., [US]) 3 December 2013 Abstract; Col. 68, lines 36-43	2-22
Y	MARIO C. MANRESA, et al, "Pharmacologic inhibition of hypoxiainducible factor (HIF)-hydroxylases ameliorates allergic contact dermatitis", ALLERGY (2019), Vol. 74(4), Pages:753-766, DOI: 10.1111/all.13655. Published online on 12 December 2018 Abstract, and Part 4, Discussion on page 763	2-22

☐ Further documents are listed in the continuation of Box C. ☒ 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
"D" document cited by the applicant in the international application
"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
01-12-2021	01-12-2021
Name and mailing address of the ISA/ Indian Patent Office Plot No.32, Sector 14,Dwarka,New Delhi-110075 Facsimile No.	Authorized officer Sankara Rao Yamala Telephone No. +91-1125300200

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2021/058243

Citation	Pub.Date	Family	Pub.Date
WO 2014102818 A1	03-07-2014	AR 094300 A1	22-07-2015
		AU 2013368843 A1	18-06-2015
		CA 2894636 A1	03-07-2014
		CN 104903295 A	09-09-2015
		EP 2935221 B1	07-02-2018
		JP 2016503052 A	01-02-2016
		KR 101733901 B1	08-05-2017
		US 2015299193 A1	22-10-2015
US 8598210 B2	03-12-2013	AU 2007265460 A1	03-01-2018
		CA 2659682 A1	03-01-2008
		CN 101506149 A	12-08-2009
		EP 2044005 A2	08-04-2009
		JP 2009541486 A	26-11-2009
		KR 101130592 B1	02-04-2012
		WO 2008002576 A2	03-01-2008