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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 June 2014 (19.06.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/092346 A1

(51) International Patent Classification:
A61K 31/573 (2006.01) *A61P 11/02* (2006.01)
A61K 31/335 (2006.01)

(21) International Application Number:
PCT/KR2013/010417

(22) International Filing Date:
15 November 2013 (15.11.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10-2012-0144524
12 December 2012 (12.12.2012) KR

(71) Applicant: **HANMI PHARM. CO., LTD.** [KR/KR]; 214, Muha-ro, Paltan-myeon, Hwaseong-si, Gyeonggi-do 445-910 (KR).

(72) Inventors: **KIM, Jin Cheul**; 3104-201, 122-10, Bulgwang-ro, Eunpyeong-gu, Seoul 122-743 (KR). **KIM, Jae Ho**; 303-ho, 37, Yuljeon-ro 101beon-gil, Jangan-gu, Suwon-si, Gyeonggi-do 440-826 (KR). **KIM, Yo Han**; #1546-52, Cheongryong-dong, Gwanak-gu, Seoul 151-844 (KR). **KIM, Yong Il**; 147-2201, 57, Hwasan-ro, Paldal-gu, Suwon-si, Gyeonggi-do 442-872 (KR). **PARK, Jae Hyun**; 311-404, 460, Yeongtong-ro, Yeongtonggu, Suwon-si, Gyeonggi-do 443-737 (KR). **WOO, Jong Soo**; 120-2303, 87, Hwasan-ro, Jangan-gu, Suwon-si, Gyeonggi-do 440-330 (KR).

(74) Agent: **FIRSTLAW P.C.**; 60 Mabang-Ro, Seocho-Ku, Seoul 137-739 (KR).

(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, KZ, LA, LC, LK, LR, LS, LT, 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, 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 2014/092346 A1

(54) Title: BITTER TASTE MASKED PHARMACEUTICAL FORMULATION COMPRISING CORTICOSTEROID, ANTIHISTAMINE AND STEVIA

(57) Abstract: The present invention relates to a bitter taste masked pharmaceutical formulation comprising: (i) corticosteroid or a pharmaceutically acceptable salt thereof; (ii) an antihistamine selected from the group consisting of olopatadine, azelastine and a pharmaceutically acceptable salt thereof; and (iii) stevia. The pharmaceutical formulation according to the present invention effectively blocks bitter taste of the active ingredients, thereby having improved taste and patient compliance, and thus can be efficiently used in the treatment of allergic rhinitis.

DESCRIPTION

BITTER TASTE MASKED PHARMACEUTICAL FORMULATION COMPRISING CORTICOSTEROID, ANTIHISTAMINE AND STEVIA

FIELD OF THE INVENTION

The present invention relates to a bitter taste masked pharmaceutical formulation comprising corticosteroid or a pharmaceutically acceptable salt thereof; antihistamine selected from the group consisting of olopatadine, azelastine and a pharmaceutically acceptable salt thereof; and stevia.

BACKGROUND OF THE INVENTION

In allergic rhinitis, an allergen interacts with and cross-links surface IgE antibodies on the surface mast cells and basophil cells. Once the mast cell-antibody-antigen complex is formed, cell-degranulation takes place which causes secretion of histamines from the mast cells or basophil cells, and thereby causing allergic reactions.

Histamine, acting on H_1-receptors, triggers pruritus, vasodilation, hypotension, flushing, headache, tachycardia, bronchoconstriction, increase in vascular permeability and potentiation of pain. Accordingly, H_1-antihistamines are clinically used in the treatment of histamine-mediated allergic conditions, *e.g.*, allergic rhinitis, allergic conjunctivitis, allergic contact dermatitis, urticaria, angioedema, pruritus (atopic dermatitis), and the like. Such antihistamines can be administered topically, through the skin, nose or eyes, or systemically.

Examples of antihistamines often used to treat or relieve the symptoms of seasonal allergic symptoms include azelastine, olopatadine, chlorpheniramine, loratadine and an isomer thereof, fexofenadine, astemizole, terfenadine, diphenhydramine, cetirizine and an isomer thereof, pseudoephedrine and the like. Among them, particular examples that are currently available in the market as nasal inhalers include azelastine (Astepro®, MEDA Pharm.), olopatadine (Patanase®, Alcon), and the like.

Corticosteroids are a class of chemicals that is closely related with cortisol, which is naturally produced in the adrenal cortex. Examples of corticosteroids include betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, deltasone, triamcinolone, mometasone, fluticasone and the like.

Corticosteroids act to block the production of substances that cause allergic reactions and inflammatory responses such as prostaglandins; however, they also cause undesirable side effects such as an increased sensitivity to infections because they interrupt leukocytes, which act as a part of the immune system by destroying foreign bodies.

Corticosteroids may be used in combination with other drugs, and prescribed for short-term or long-term use. In the case where corticosteroids are absorbed systemically for a long period of time, it may cause undesirable side effects such as increased appetite and weight gain; fat deposits in chest, face and the like; a build-up of water or salt in the body which may be developed into edema or dropsy; hypertension; diabetes; osteoporosis; cataracts; etc. Thus, corticosteroids may be used in the form of nasal spray and drop for the treatment of nasal diseases and, similarly, in the form of inhaler for the treatment of trachea-bronchial diseases to prevent corticosteroids from being absorbed systemically in the body. Examples of corticosteroids in the form of nasal spray available in the market include mometasone, fluticasone, budesonide, etc.

In the treatment of seasonal allergic rhinitis, a synergistic effect can be expected when a combination of antihistamine and corticosteroids are applied via nasal cavity. Mometasone is a long-acting corticosteroid used to treat allergic rhinitis which alleviates symptoms of rhinitis in patients; whereas azelastine is a rapid-acting which alleviates the symptoms immediately. Thus, the combination formulation of these two drugs is an effective medication for the treatment of allergic rhinitis having both long-acting and rapid-acting characteristics.

In the development of a combined formulation, however, it is difficult to prepare a formulation using azelastine and a pharmaceutically acceptable salt thereof because of its bitter taste which makes patients hard to take it. When a patient takes the formulation via inhalation by using a nasal spray, the formulation passes through the pharynx, and thereby causing unpleasant taste and irritation.

Meda AB, the pharmaceutical company who developed the Azelastine nasal spray, have disclosed a taste masked pharmaceutical composition using sucralose to improve the bitter taste of azelastine (Korean Laid-Open Patent No. 2007-0104884). Nevertheless, Astepro 0.15% (Azelastine HCl), the nasal spray developed by using the above composition still caused displeasing bitter taste of azelastine.

Meanwhile, *Stevia rebaudiana* is an herbaceous perennial in the Chrysanthemum family that is native to Paraguay in South America; its sweet ingredients, whose main ingredient is steviol glycoside, are mostly found in the leaves. Steviol glycoside is about 200 to 300 times sweeter than sucrose and known to contain almost no calories.

Accordingly, the present inventors have discovered a combination nasal spray for nasal administration having improved taste and patient compliance by using a certain amount of stevia as a sweetener, and thus accomplished the present invention.

SUMMARY OF THE INVENTION

Accordingly, it is an object of the present invention to provide a bitter taste masked pharmaceutical formulation comprising corticosteroid, an antihistamine and stevia.

In accordance with one object of the present invention, there is provided a bitter taste masked pharmaceutical formulation comprising:

(i) corticosteroid or a pharmaceutically acceptable salt thereof;

(ii) an antihistamine selected from the group consisting of olopatadine, azelastine and a pharmaceutically acceptable salt thereof; and

(iii) stevia (*Stevia rebaudiana*).

The inventive pharmaceutical formulation comprises stevia as a sweetener, which can effectively block the bitter taste of azelastine and olopatadine, and also provide good nasal sensation when administered via intranasal route, and thus can be effectively used as a pharmaceutical formulation for nasal delivery in the treatment of allergic rhinitis.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a bitter taste masked pharmaceutical formulation comprising: (i) corticosteroid or a pharmaceutically acceptable salt thereof; (ii) an antihistamine selected from the group consisting of olopatadine, azelastine and a pharmaceutically acceptable salt thereof; and (iii) stevia.

In the present invention, the corticosteroid or a pharmaceutically acceptable salt thereof may be mometasone, fluticasone, budesonide, or a pharmaceutically acceptable salt or free base thereof, preferably mometasone or a pharmaceutically acceptable salt thereof.

The corticosteroid may be comprised in an amount of 0.01 to 1 weight%, based on the total weight of the formulation.

In the present invention, the antihistamine may be selected from the group consisting of olopatadine, azelastine and a pharmaceutically acceptable salt thereof, and particular examples include olopatadine hydrochloride or azelastine hydrochloride.

The antihistamine may be comprised in an amount of 0.1 to 20 weight%, preferably 0.1 to 10 weight%, based on the total weight of the formulation.

Additionally, any type of stevia known in the art may be used in the present invention, *e.g.*, steviol glycoside, enzymatically modified stevia or a mixture thereof. The steviol glycoside is a sweetener, which is prepared by extracting the sweet ingredient of stevia from the plant and subjecting the stevia extract to a distillation process; for example, subjecting *Stevia rebaudiana* to extraction and purification by using ethanol or purified water as a solvent. Also, the enzymatically modified stevia is stevia with improved sweetness whose main ingredient of sweet taste is α-glucosylstevioside, that is obtainable by subjecting *Stevia rebaudiana* to an enzymatic treatment; preferably, extracting stevia by using ethanol or purified water as a solvent, and subjecting the stevia extract to an enzymatic treatment using an enzyme such as α-glucosyltransferase to obtain α-glucosylstevioside and α-glucosyl rebaudioside A, followed by purifying the products thus obtained.

The stevia may be comprised in an amount of 0.1 to 5 weight%, preferably 0.5 to 2.0 weight%, *e.g.*, 1.0 weight%. If the amount of the steviol glycoside and the enzymatically modified stevia is less than 0.1 weight%, it may not give bitter taste masking effects; and when the amount of the enzymatically modified stevia

exceeds 5 weight%, it may cause severe irritation in the mucosa membranes of the nasal cavity.

Moreover, the pharmaceutical formulation of the present invention may further comprise thaumatin as a sweetener.

The pharmaceutical formulation in accordance with the present invention may be a liquid formulation, preferably a nasal spray-type liquid formulation.

The pharmaceutical formulation in accordance with the present invention may comprise pharmaceutically acceptable additives, *e.g.*, carriers or excipients, particularly one or more of pharmaceutically acceptable carriers or excipients useful for preparing a nasal spray formulation.

Further, the pharmaceutical formulation in accordance with the present invention may further comprise, besides the sweetener that masks bitter taste of an antihistamine such as azelastine and olopatadine, a viscosity increasing agent to reduce or prevent the formulation to reach the pharynx via postnasal drip when the formulation is administered to the nasal cavity. Examples of the viscosity increasing agent may be selected from the group consisting of cellulose derivatives such as microcrystalline cellulose and carboxymethyl cellulose, gums, povidone and a mixture thereof, but not limited thereto.

In accordance with one embodiment of the present invention, the nasal spray-type liquid formulation may comprise a pharmaceutically acceptable carrier or excipient which may be useful for preparing the formulation as a nasal spray-type liquid formulation, *e.g.*, one or more components selected from the group consisting of a solvent, a preservative, a viscosity increasing agent, a pH modifier, an additional sweetening agent, a solubilizing agent and a mixture thereof.

The solvent may be a purified water.

The preservative may be selected from the group consisting of benzalkonium chloride, potassium sorbate, sodium benzonate and a mixture thereof, but not limited thereto.

The pH modifier may be selected from the group consisting of citric acid, succinic acid, malic acid, sodium citrate, and a mixture thereof, but not limited thereto.

The additional sweetening agent may be selected from the group consisting of thaumatin, saccharin, xylitol, aspartame, potassium acesulfame and a mixture thereof, but not limited thereto.

The solubilizing agent may be polysorbate, glycerin and a mixture thereof,

but not limited thereto.

The pharmaceutical formulation of the present invention comprises stevia as a sweetening agent in an amount of 0.1 to 5 weight%, based on the total weight of the formulation, which can effectively block bitter taste of azelastine and olopatadine, and also provide good nasal sensation when administered via intranasal route, and thus can be effectively used as a pharmaceutical formulation for nasal delivery in the treatment of allergic rhinitis.

EXAMPLES

Hereinafter, the present invention is described more specifically by the following Examples. However, these are provided only for illustration purposes, and are not intended to limit the scope of the present invention.

Example 1: Azelastine Hydrochloride Nasal Spray Suspension Comprising Mometasone

A nasal spray suspension was prepared in accordance with the ingredients described in Table 1.

A viscosity increasing agent, Avicel RC-591 (FMC, USA), and glycerin (Seojin Chemical) were added to sterile purified water and dispersed (Mixture 1). Sterile purified water was poured in a separate container, added with azelastine hydrochloride (Aarti), benzalkonium chloride (Dolder AG), citric acid hydrate (DSM), sodium citrate hydrate (Jungbunzlauer GMBH), disodium edetate hydrate (Ridel-de Haen), D-sorbitol (Roquette), taumatin (Natex) and steviol glycoside (Choheung Corp.), and stirred to dissolve the ingredients (Mixture 2). Sterile purified water was placed in a separate container, added with mometasone furoate (Cipla) and polysorbate 80 (Croda), and dispered (Mixture 3). First, Mixture 1 and Mixture 2 prepared above were admixed and stirred, and then Mixture 3 was added thereto, followed by stirring. Sterile purified water was added to the final mixture up to the final volume to obtain the nasal spray suspension.

Example 2: Azelastine Hydrochloride Nasal Spray Suspension Comprising Mometasone

A nasal spray suspension was prepared in accordance with the ingredients described in Table 1 by repeating the procedures of Example 1, except for using enzymatically modified stevia (Choheung Corp.) instead of steviol glycoside.

[Table 1]

Ingredient (w/v%)	Example 1	Example 2
Mometasone furoate	0.05	0.05
Azelastine hydrochloride	0.14	0.14
Avicel RC-591	2.0	2.0
Glycerin	2.1	2.1
Disodium edetate hydrate	0.1	0.1
Citric acid hydrate	0.2	0.2
Sodium citrate hydrate	0.28	0.28
Polysorbate 80	0.01	0.01
Benzalkonium chloride	0.02	0.02
D-sorbitol	6.6	6.6
Thaumatin	0.25	0.25
Steviol glycoside	1.0	-
Enzymatically modified stevia	-	1.0
Distilled water	Residual quantity	Residual quantity

Example 3: Olopatadine Hydrochloride Nasal Spray Suspension Comprising Mometasone

A nasal spray suspension was prepared in accordance with the ingredients described in Table 2 by repeating the procedures of Example 1, except for using olopatadine hydrochloride instead of azelastine hydrochloride.

Example 4: Olopatadine Hydrochloride Nasal Spray Suspension Comprising Mometasone

A nasal spray suspension was prepared in accordance with the ingredients described in Table 2 by repeating the procedures of Example 2, except for using olopatadine hydrochloride instead of azelastine hydrochloride.

[Table 2]

Ingredient (w/v%)	Example 3	Example 4
Mometasone furoate	0.05	0.05
Olopatadine hydrochloride	6.65	6.65
Avicel RC-591	2.0	2.0
Glycerin	2.1	2.1

Disodium edetate hydrate	0.1	0.1
Citric acid hydrate	0.2	0.2
Sodium citrate hydrate	0.28	0.28
Polysorbate 80	0.01	0.01
Benzalkonium chloride	0.02	0.02
D-sorbitol	6.6	6.6
Thaumatin	0.25	0.25
Steviol glycoside	1.0	-
Enzymatically modified stevia	-	1.0
Distilled water	Residual quantity	Residual quantity

Example 5: Azelastine Hydrochloride Nasal Spray Suspension Comprising Mometasone

A nasal spray suspension was prepared by repeating the procedures of Example 1, except for not adding thaumatin.

Comparative Example 1: Azelastine Hydrochloride Nasal Spray Suspension Comprising Mometasone

A nasal spray suspension was prepared with the ingredients described in Table 3 by repeating the procedures of Example 1, except for not adding steviol glycoside.

Comparative Examples 2 to 4: Azelastine Hydrochloride Nasal Spray Suspensions Comprising Mometasone

Nasal spray suspensions were prepared with the ingredients described in Table 3 by repeating the procedures of Example 1, except for using each of the artificial sweeteners saccharin, xylitol and aspartame, respectively, instead of steviol glycoside.

Comparative Example 5: Azelastine Hydrochloride Nasal Spray Suspension Comprising Mometasone

A nasal spray suspension was prepared with the ingredients described in Table 3 by repeating the procedures of Example 1, except for using olopatadine hydrochloride instead of azelastine hydrochloride, and using aspartame instead of

stevio glycoside.

[Table 3]

Ingredient (w/v%)	Comparative Example 1	Comparative Example 2	Comparative Example 3	Comparative Example 4	Comparative Example 5
Mometasone furoate	0.05	0.05	0.05	0.05	0.05
Azelastine hydrochloride	0.14	0.14	0.14	0.14	-
Olopatadine hydrochloride	-	-	-	-	6.65
Avicel RC-591	2.0	2.0	2.0	2.0	2.0
Glycerin	2.1	2.1	2.1	2.1	2.1
Disodium edetate hydrate	0.1	0.1	0.1	0.1	0.1
Citric acid hydrate	0.2	0.2	0.2	0.2	0.2
Sodium citrate hydrate	0.28	0.28	0.28	0.28	0.28
Polysorbate 80	0.01	0.01	0.01	0.01	0.01
Benzalkonium chloride	0.02	0.02	0.02	0.02	0.02
D-sorbitol	6.6	6.6	6.6	6.6	6.6
Thaumatin	0.25	0.25	0.25	0.25	0.25
Saccharin	-	1.0	-	-	-
Xylitol	-	-	1.0	-	-
Aspartame	-	-	-	1.0	1.0
Distilled water	Residual quantity	Residual quantity	Residual quantity	Residual quantity	Residual quantity

Comparative Examples 6 and 7: Azelastine Hydrochloride Nasal Spray Suspensions Comprising Mometasone

Nasal spray suspensions were prepared by repeating the procedures of Examples 1 and 2 each, except for using 0.05 weight% of steviol glycoside and enzymatically modified stevia in Examples 1 and 2, respectively.

Comparative Examples 8 and 9: Azelastine Hydrochloride Nasal Spray Suspensions Comprising Mometasone

Nasal spray suspensions were prepared by repeating the procedures of Examples 1 and 2 each, except for using 10 weight% of steviol glycoside and enzymatically modified stevia in Examples 1 and 2, respectively.

Test Example 1: Evaluation of Bitter Taste (Nasal Sensation Test)

Nasal spray suspensions prepared in Examples 1, 2 and 5, and Comparative Examples 1 to 4, and 6 to 9 were filtered through 100 mesh screen, and packaged in a high density polyethylene container having a Valois pump which was designed to administer 0.1 mL of the suspension composition into the nasal cavity to prepare a pharmaceutical formulation for nasal delivery.

In order to conduct the sensory evaluation test for comparing bitter taste masking effects of different kinds of sweeteners, the pharmaceutical formulations for nasal delivery were administered to 16 test participants, and the degree of bitterness and the duration of bitterness in the mouth were evaluated in combination by measuring them in accordance with the following criteria and averaging the results:

- Degree of bitterness -

1: almost no bitterness

2: somewhat bitter

3: bitter

4: strongly bitter

5: too bitter to be used

- Duration of bitterness -

1: substantially no duration

2: lasted less than 10 seconds

3: lasted less than 60 seconds

4: lasted less than 5 minutes

5: lasted more than 1 hour.

The results are shown in Table 4 below.

[Table 4]

	Degree of bitterness	Duration of bitterness in the mouth
Example 1	1.1	1.2
Example 2	1.1	1.3
Example 5	1.2	1.2
Comparative Example 1	4.1	3.6
Comparative Example 2	4.3	3.3

Comparative Example 3	4.5	3.8
Comparative Example 4	4.0	3.8
Comparative Example 6	4.0	3.7
Comparative Example 7	4.0	3.7

As shown in Table 4 above, the degree of bitterness and the duration of bitterness of the inventive pharmaceutical formulation for nasal delivery comprising steviol glycoside or enzymatically modified stevia decreased by about 1/4 and 1/3, respectively, as compared with those of the conventional products not containing sweetener or using conventional artificial sweeteners, and thus showing improved bitter taste masking effects. Also, the inventive pharmaceutical formulation for nasal delivery prepared in Example 5 comprising stevia, as its only sweetener, showed similar bitter taste masking effects as that of Example 1.

Meanwhile, the pharmaceutical formulations for nasal delivery prepared in Comparative Examples 6 and 7 comprising stevia in an amount of 0.05 weight%, based on the total weight of the formulation, showed the degree of bitterness (4.0) and the duration of bitterness (3.7) similar to those of Comparative Example 1. When the pharmaceutical formulations for nasal delivery prepared in Comparative Examples 8 and 9 comprising stevia in an amount of 10 weight%, based on the total weight of the formulation, were administered to the test participants, all the participants complained of irritation in the nasal mucous membrane, and thus it was concluded that the pharmaceutical formulations prepared in Comparative Examples 8 and 9 were not appropriate for use.

Test Example 2: Evaluation of Bitter Taste (Nasal Sensation Test)

The test methods of Test Example 1 were used to compare bitter taste masking effects of the pharmaceutical formulations for nasal delivery prepared in Examples 3 and 4, and Comparative Example 5. The results are shown in Table 5 below.

[Table 5]

	Degree of bitterness	Duration of bitterness
Example 3	1.1	1.2
Example 4	1.2	1.4

Comparative Example 5	3.8	3.6

As shown in Table 5 above, the degree of bitterness and the duration of bitterness measured for the inventive pharmaceutical formulation for nasal delivery comprising steviol glycoside or enzymatically modified stevia, as its sweetener, were reduced by 1/3 as compared with the pharmaceutical formulation containing the conventional artificial sweetener, indicating that they have improved bitter taste masking effects.

Thus, in the preparation of nasal spray-type formulation comprising mometasone, and azelastine or olopatadine, the use of steviol glycoside or enzymatically modified stevia, as its sweetener, allows improved bitter taste masking effects as compared with the use of conventional artificial sweeteners, thereby enhancing patient compliance; therefore, it can be effectively used in the treatment of allergic rhinitis.

WHAT IS CLAIMED IS:

1. A bitter taste masked pharmaceutical formulation comprising:

(i) corticosteroid or a pharmaceutically acceptable salt thereof;

(ii) an antihistamine selected from the group consisting of olopatadine, azelastine and a pharmaceutically acceptable salt thereof; and

(iii) stevia.

2. The pharmaceutical formulation of claim 1, wherein the corticosteroid is mometasone, fluticasone, budesonide, or a pharmaceutically acceptable salt or free base thereof.

3. The pharmaceutical formulation of claim 1, wherein the corticosteroid is mometasone.

4. The pharmaceutical formulation of claim 1, wherein the corticosteroid is comprised in an amount of 0.01 to 1 weight%, based on the total weight of the formulation.

5. The pharmaceutical formulation of claim 1, wherein the antihistamine is comprised in an amount of 0.1 to 20 weight%, based on the total weight of the formulation.

6. The pharmaceutical formulation of claim 1, wherein the stevia is steviol glycoside, enzymatically modified stevia or a mixture thereof.

7. The pharmaceutical formulation of claim 6, wherein the enzymatically modified stevia is prepared by subjecting a stevia extract to an enzymatic treatment using an α-glucosyltransferase to obtain α-glucosylstevioside and α-glucosyl rebaudioside A, followed by purification.

8. The pharmaceutical formulation of claim 1, wherein the stevia is comprised in an amount of 0.1 to 5 weight%, based on the total weight of the formulation.

9. The pharmaceutical formulation of claim 1, wherein the formulation is a liquid formulation.

10. The pharmaceutical formulation of claim 9, wherein the liquid formulation is a nasal spray-type liquid formulation.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2013/010417

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/573(2006.01)i, A61K 31/335(2006.01)i, A61P 11/02(2006.01)i

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 31/573; A61K 9/68; A61L 9/04; A61K 31/70; A61K 31/55; A61K 9/50; A61K 31/56; A61K 31/7012; A61K 36/00; A61K 31/335; A61P 11/02

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & Keywords: corticosteroid, mometasone, fluticasone, budesonide, antihistamine, olopatadine, azelastine, stevia, α-glucosyltransferase

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2007-0020330 A1 (DANG, P. G. et al.) 25 January 2007 See claims 1-3 and 8; and paragraphs [0025]-[0030], [0083] and [0091].	1-10
Y	US 2005-0118273 A1 (SASAKI, Y. et al.) 02 June 2005 See paragraph [0140].	1-10
A	US 2006-0216353 A1 (LIVERSIDGE, G. et al.) 28 September 2006 See claims 1, 2, 4, 10 and 19; and paragraphs [0138]-[0140].	1-10
A	US 2006-0025391 A1 (LULLA, A. et al.) 02 February 2006 See claims 1, 4, 7 and 20; and paragraph [0042].	1-10
A	US 2011-0189311 A1 (TOZUKA, Y. et al.) 04 August 2011 See claims 1 and 5; and paragraphs [0043]-[0050].	1-10

☐ 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
"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
29 January 2014 (29.01.2014)	**29 January 2014 (29.01.2014)**

Name and mailing address of the ISA/KR
Korean Intellectual Property Office
189 Cheongsa-ro, Seo-gu, Daejeon Metropolitan City, 302-701, Republic of Korea
Facsimile No. +82-42-472-7140

Authorized officer
CHOI, Sung Hee
Telephone No. +82-42-481-8740

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR2013/010417

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2007-0020330 A1	25/01/2007	AU 2005-309657 A1	01/06/2006
		CA 2588338 A1	01/06/2006
		CA 2588338 C	28/05/2013
		CN 101098714 A0	02/01/2008
		CN 101098714 B	28/09/2011
		EP 1827499 A1	05/09/2007
		EP 2377557 A2	19/10/2011
		EP 2377557 A3	14/11/2012
		EP 2486942 A1	15/08/2012
		EP 2522365 A1	14/11/2012
		JP 2008-521812 A	26/06/2008
		JP 2013-047253 A	07/03/2013
		KR 10-2007-0104884 A	29/10/2007
		US 2006-0110331 A1	25/05/2006
		US 2010-0152147 A1	17/06/2010
		US 2012-0083479 A1	05/04/2012
		US 8071073 B2	06/12/2011
		WO 2006-058022 A1	01/06/2006
		WO 2007-061454 A1	31/05/2007
US 2005-0118273 A1	02/06/2005	AT 454827 T	15/01/2010
		AU 2002-355012 B2	15/05/2008
		CA 2470351 A1	22/05/2003
		CA 2470351 C	16/08/2011
		CN 1589106 A	02/03/2005
		DE 60235117 D1	04/03/2010
		EP 1454534 A1	08/09/2004
		EP 1454534 A4	22/02/2006
		EP 1454534 B1	13/01/2010
		ES 2335579 T3	30/03/2010
		JP 3885195 B2	21/02/2007
		KR 10-0944814 B1	02/03/2010
		KR 10-2005-0044481 A	12/05/2005
		NZ 533501 A	30/06/2008
		WO 03-041509 A1	22/05/2003
US 2006-0216353 A1	28/09/2006	AU 2006-226887 A1	28/09/2006
		BR PI0609700 A2	20/04/2010
		CA 2602341 A1	28/09/2006
		CN 101180038 A	14/05/2008
		EA 200702049 A1	28/02/2008
		EP 1868578 A2	26/12/2007
		IL 186159 D0	20/01/2008
		JP 2008-534509 A	28/08/2008
		KR 10-2007-0121786 A	27/12/2007
		MX 2007011772 A	05/12/2007
		NO 20075398 A	14/12/2007
		US 8003127 B2	23/08/2011
		WO 2006-102494 A2	28/09/2006

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR2013/010417

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		WO 2006-102494 A3	25/01/2007
		ZA 200708544 A	25/03/2009
US 2006-0025391 A1	02/02/2006	AP 200403192 D0	31/12/2004
		AT 428428 T	15/05/2009
		AU 2003-244799 A1	31/12/2003
		AU 2003-244799 B2	10/09/2009
		AU 2009-243420 A1	24/12/2009
		AU 2009-243420 B2	11/10/2012
		AU 2009-243422 A1	17/12/2009
		AU 2009-243422 B2	29/03/2012
		BR 0312128 A	05/04/2005
		CA 2489427 A1	24/12/2003
		CA 2489427 C	25/09/2012
		CA 2779630 A1	24/12/2003
		CA 2779633 A1	24/12/2003
		CN 1674910 A	28/09/2005
		CR 7654 A	22/10/2007
		DE 60327203 D1	28/05/2009
		DK 1519731 T3	03/08/2009
		EP 1519731 A1	06/04/2005
		EP 1519731 B1	15/04/2009
		EP 2072051 A1	24/06/2009
		EP 2075000 A1	01/07/2009
		ES 2324910 T3	19/08/2009
		GB 0213739 D0	24/07/2002
		GB 2389530 A	17/12/2003
		GB 2389530 B	10/01/2007
		GE P120105143 B	25/01/2011
		IL 165771 D0	15/01/2006
		IL 216931 D0	31/01/2012
		IL 216932 D0	31/01/2012
		KR 10-1119895 B1	22/02/2012
		KR 10-1301061 B1	28/08/2013
		KR 10-1301558 B1	04/09/2013
		KR 10-2005-0024362 A	10/03/2005
		KR 10-2011-0113781 A	18/10/2011
		KR 10-2011-0113782 A	18/10/2011
		MA 27285 A1	01/04/2005
		MX PA04012666 A	30/09/2005
		NZ 537246 A	28/09/2007
		NZ 574658 A	30/09/2010
		PL 373001 A1	08/08/2005
		PT 1519731 E	13/07/2009
		RU 2005100781 A	10/08/2005
		RU 2361593 C2	20/07/2009
		SI 1519731 T1	31/10/2009
		US 2009-0291143 A1	26/11/2009
		US 2009-0318397 A1	24/12/2009
		US 2010-0331289 A1	30/12/2010

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR2013/010417

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		US 2013-0029951 A1	31/01/2013
		US 2013-0029952 A1	31/01/2013
		US 8163723 B2	24/04/2012
		US 8168620 B2	01/05/2012
		US 8304405 B2	06/11/2012
		US 8318709 B2	27/11/2012
		WO 03-105856 A1	24/12/2003
		ZA 200500331 A	26/07/2006
US 2011-0189311 A1	04/08/2011	EP 2292214 A1	09/03/2011
		JP 2011-051938 A	17/03/2011