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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 October 2020 (22.10.2020)

WIPO | PCT

(10) International Publication Number
WO 2020/212982 A1

(51) International Patent Classification:
A61K 31/05 (2006.01) *A61K 31/606* (2006.01)
A61K 31/635 (2006.01) *A61P 1/00* (2006.01)
A61K 31/58 (2006.01) *A61K 9/00* (2006.01)

(21) International Application Number:
PCT/IL2020/050441

(22) International Filing Date:
16 April 2020 (16.04.2020)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/834,992 17 April 2019 (17.04.2019) US

(71) Applicant: **SOL-GEL TECHNOLOGIES LTD.** [IL/IL]; 7 Golda Meir St., Weizmann Science Park, 7403650 Ness Ziona (IL).

(72) Inventor: **ARKIN, Moshe**; 26 Derech Haganim Street, 4691000 Kfar Shmaryahu (IL).

(74) Agent: **COHEN, Mark S.** et al.; Pearl Cohen Zedek Latzer Baratz, P.O. Box 7198, 6107121 Tel Aviv (IL).

(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, 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).

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

WO 2020/212982 A1

(54) Title: TREATMENT OF GASTROINTESTINAL DISORDERS WITH RECTAL TAPINAROF COMPOSITIONS

(57) Abstract: Provided herein is a rectal composition for the treatment of GI disorders, comprising a therapeutically effective amount of tapinarof and a carrier suitable for rectal administration. The rectal composition optionally further comprises at least one additional active agent. Also provided is a combination composition optionally further comprising a vasoconstrictor. Exemplary tapinarof rectal compositions are tapinarof, tapinarof-mesalamine, tapinarof- mesalamine-pramoxine and tapinarof-budesonide compositions.

TREATMENT OF GASTROINTESTINAL DISORDERS WITH RECTAL TAPINAROF COMPOSITIONS

FIELD OF THE INVENTION

[001] The present invention, in some embodiments thereof, relates to pharmaceutical compositions, more particularly to rectal compositions comprising tapinarof.

[002] The compositions of this invention are useful for the treatment, prevention or amelioration of anal, rectal or distal gastrointestinal (GI) disorders amenable to treatment by rectal administration of tapinarof compositions.

BACKGROUND

[003] Anal, rectal and distant GI disorders comprise Chron's disease, irritable bowel syndrome (IBS), ulcerative colitis, proctosigmoiditis, ulcerative proctitis, hemorrhoids, perianal itching, anal fissures, perianal abscesses, anal fistulas and perianal infections.

[004] Current treatments of GI disorders include administration of anti-inflammatory drugs such as corticosteroids, amino salicylates (mesalamine, balsalazide and olsalazine), immune system suppressors such as azathioprine, mercaptopurine, cyclosporine and methotrexate and antibiotics such as ciprofloxacin and metronidazole.

[005] However, the presently available medications are less than optimal in curing chronic and acute GI disorders and result in limited success.

[006] Thus, there exists an unmet need for a novel approach in the treatment of GI disorders providing improved efficacy, thus making possible the long-term treatment of these disorders.

SUMMARY OF THE INVENTION

[007] This invention provides a rectal composition comprising tapinarof and optionally further comprising at least one additional active agent.

[008] Also provided are methods of treatment of GI disorders by rectal administration to a subject in need thereof of a composition comprising a therapeutically effective amount of tapinarof and optionally at least one additional active agent.

DETAILED DESCRIPTION OF THE INVENTION

[009] This invention provides a novel approach for the treatment of anal, rectal and distant GI disorders, based on the administration to a subject in need thereof a therapeutically effective amount of a rectal composition comprising tapinarof, optionally further comprising at least one additional active agent.

[0010] In some embodiments, there is provided a rectal composition comprising a therapeutically effective amount of tapinarof and a carrier suitable for rectal administration.

[0011] In some other embodiments, the rectal composition may optionally further comprise a therapeutically effective amount of at least one additional active agent.

[0012] The at least one additional active agent is selected from anti-inflammatory drugs, such as an NSAID or a corticosteroid, amino salicylates such as mesalamine, balsalazide and olsalazine, immune system suppressors such as azathioprine, mercaptopurine, cyclosporine and methotrexate, antibiotics such as ciprofloxacin and metronidazole, vasoconstrictors such as phenylephrine and local anesthetics such as lidocaine and pramoxine.

[0013] Each combination of tapinarof and at least one additional active agent is a separate embodiment.

[0014] Tapinarof (3,5-dihydroxy-4-isopropyl-trans-stilbene, benvitimod, GSK2894512) is a first-in-class drug, whose mechanism is not yet fully understood. It is being developed by Glaxo Smith Kline (Stiefel, a GSK company) and Dermavant as a topical drug for treatment of mild to moderate plaque psoriasis and atopic dermatitis. Tapinarof was shown in both mouse models and in vitro human skin studies to inhibit specific proinflammatory mediators, including interleukin-6 and interleukin-17A, and enhance skin barrier function (J Invest Dermatol. 2017 Oct;137[10]:2110-9).

[0015] Tapinarof and the optional at least one additional active agent are formulated in a rectal composition or administered independently.

Rectal Compositions

[0016] Provided herein are rectal compositions, combinations, kits and articles of manufacture for treating GI disorders comprising tapinarof and optionally at least one additional active agent, selected from anti-inflammatory drugs such as corticosteroids and NSAIDs, amino salicylates such as mesalamine, balsalazide and olsalazine, immune system suppressors such as azathioprine,

mercaptopurine, cyclosporine and methotrexate, antibiotics such as ciprofloxacin and metronidazole, phenylephrine and local anesthetics like lidocaine and pramoxine.

[0017] Tapinarof and the selected at least one additional active agent may be combined in various ways, providing a large number of possible combinations. Each combination is a separate embodiment.

Exemplary rectal tapinarof and tapinarof combination compositions

[0018] Several exemplary rectal tapinarof compositions are tapinarof, tapinarof-mesalamine, tapinarof-mesalamine-pramoxine and tapinarof-budesonide compositions.

[0019] Each of the compositions below is a separate embodiment.

[0020] Some of these compositions are described in Examples 1-4.

1. A tapinarof composition comprising from about 0.1% w/w to about 20.0% w/w tapinarof (Example 1).
2. A tapinarof-mesalamine combination composition comprising from about 0.1% w/w to about 20.0% w/w tapinarof and from about 0.25% w/w to about 20.0% w/w mesalamine (see Example 2).
3. A tapinarof-budesonide combination composition comprising from about 0.1% w/w to about 20.0% w/w tapinarof and from about 0.01% w/w to about 2.0% w/w budesonide (see Example 3).
4. A tapinarof-mesalamine-pramoxine combination composition comprising from about 0.1% w/w to about 20.0% w/w tapinarof, from about 0.25% w/w to about 20.0% w/w mesalamine and from about 0.25% w/w to about 2.0% w/w pramoxine (see Example 4).

[0021] The compositions, combinations and articles of manufacture of this invention can be administered rectally using a variety of compositions. The administration route is rectal and the preferred formulations are a rectal enema, a rectal suppository, a rectal a foam, a cream, a lotion, or a gel.

[0022] The active agents in the combination compositions are included in an amount effective for treating, preventing or reducing the GI disorder symptoms. The concentration of the active agents in the composition will depend on absorption, inactivation, excretion rates of the active agent, the synergistic or additive effects, the dosage schedule, and amount administered as well as other

factors known to those of skill in the art. Generally, the dosages and concentrations will be lower, typically at least about or at 5 to 10% lower but up to about or at 15, 20, 25, 30, 35, 40, 50, 90 or 95% lower than the amount of same active agents in the marketed single drug currently administered or being developed for the treatment of GI disorders. The dosage and regimen of administration may be determined by dose finding studies, as known in the art.

[0023] Exemplary dosages, strengths and concentrations of tapinarof in the tapinarof rectal compositions, is between 0.1% to 20% w/w. In another embodiment, the concentration can be 0.1%, 0.25%, 0.5%, 1%, 2%, 3%, 5%. 10%, 15% or 20% w/w. In another embodiment, the concentration of tapinarof in the compositions of this invention is between 0.1% to 5% w/w. In another embodiment, between 1% to 20% w/w, in another embodiment between 1% to 10% w/w. In another embodiment, between 1% to 5% w/w.

[0024] Exemplary dosages, strengths and concentrations of mesalamine in the tapinarof - mesalamine rectal compositions or in the tapinarof-mesalamine-pramoxine rectal composition is between 0.25% to 20% w/w. In another embodiment, the concentration of mesalamine can be 0.25%, 0.5%, 1%, 2%, 3%, 5%. 10%, 15% or 20% w/w. In another embodiment, the concentration of mesalamine in the compositions of this invention is between 0.25% to 5% w/w. In another embodiment, between 1% to 20% w/w, in another embodiment between 1% to 10% w/w. In another embodiment, between 1% to 5% w/w.

[0025] Exemplary dosages, strengths and concentrations of budesonide in the tapinarof - budesonide rectal compositions is between 0.01% to 2.0% w/w. In another embodiment, the concentration of budesonide can be 0.01%, 0.03%, 0.05%, 1%, 1.5% or 2.0% w/w. In another embodiment, the concentration of budesonide in the compositions of this invention is between 0.01% to 0.05% w/w. In another embodiment, between 0.05% to 1% w/w, in another embodiment between 0.05% to 1.5% w/w. In another embodiment, between 1% to 2.0% w/w.

[0026] Exemplary dosages, strengths and concentrations of pramoxine in the tapinarof - mesalamine-pramoxine rectal compositions is between 0.25% to 2.0% w/w. In another embodiment, the concentration of pramoxine can be 0.25%, 0.5%, 0.7%, 1%, 1.5% or 2.0% w/w. In another embodiment, the concentration of pramoxine in the compositions of this invention is between 0.25% to 0.7% w/w. In another embodiment, between 0.25% to 1% w/w, in another embodiment between 0.5% to 1.5% w/w. In another embodiment, between 0.5% to 2.0% w/w

[0027] The frequency of administration can be determined empirically. Exemplary frequencies

are once daily, twice daily, four times daily, weekly, bi-weekly or monthly. Typical administration frequencies of the rectal compositions of this invention are once daily to four times daily.

[0028] Dosage frequencies can be gradually attenuated over time and maintained at a steady dose suitable for long-term - six months, 1 year, 5 years, 10 years or more, up to lifelong administration to control the symptoms of the GI disorders. For example, dosage administration can begin at from four times a day, twice a day, to once a day, to four times a day, to two times a week, to once a week, to once every two weeks or less frequent than once every two weeks.

[0029] Pharmaceutical carriers or vehicles suitable for preparation of the rectal compositions provided herein include any such carriers known to those skilled in the art to be suitable for this particular mode of administration.

[0030] The resulting composition may be a lotion, a solution, a suspension, an emulsion or the like and is formulated as enemas, suppositories, foams, creams, gels, ointments, tapes, emulsions, solutions, elixirs, lotions, suspensions, tinctures, pastes, aerosols, sprays or any other formulation suitable for rectal administration.

[0031] The administration route is rectal and the preferred formulations are the rectal enema, the rectal suppository, the rectal foam, the cream, the lotion and the gel.

[0032] The active agents may be formulated as the sole pharmaceutically active agent in the composition or may be combined with at least one additional active agent. The active agents are included in the carrier in an amount sufficient to exert a therapeutically useful effect i.e., treatment, prevention and/or amelioration of the symptoms of GI disorders, with minimal or no toxicity or other side effects. Generally, emollient or lubricating vehicles that help hydrate the tissues are more preferred than volatile vehicles, such as ethanol, that dry the tissues. Examples of suitable bases or vehicles for preparing compositions for use with these compositions are petrolatum, petrolatum, volatile silicones, lanolin, cold cream and hydrophilic ointment.

[0033] Suitable pharmaceutically acceptable vehicles for rectal application include rectal suppositories, enemas, lotions, creams, rectal foams, solutions, gels, tapes and the like. Generally, the vehicle is either organic in nature or an aqueous emulsion and capable of having the selected compound or compounds, which may be micronized, dispersed, suspended or dissolved therein. The vehicle may include pharmaceutically-acceptable emollients, local anesthetics, moisturizers, including lactic acid, ammonium lactate and urea, skin penetration enhancers, coloring agents,

fragrances, emulsifiers, thickening agents, vegetable oils, essential oils, zinc oxide and solvents.

Methods of treatment

[0034] According to an aspect of the invention, there is provided a method of treatment of GI disorders by rectal administration to a subject in need thereof of a composition comprising tapinarof, optionally at least one additional active agent and optionally a vasoconstrictor. In some embodiments, the effective amount is a therapeutically effective amount of the active agents, namely an amount which will cure, treat, mitigate or prevent GI disorders.

[0035] In some embodiments, co-administration of the active agents exhibits an additive and/or synergistic effect while treating, preventing or alleviating GI disorders.

[0036] In some other embodiments, the co-administration may be made either by administration of a single combination composition, or alternatively by separate administration of a first composition comprising tapinarof and a second composition comprising at least one additional active agent.

Regimen of Administration of the Rectal Tapinarof Compositions

[0037] Therapeutically effective concentrations of active agents in the compositions of this invention for treatment, prevention or amelioration of the symptoms manifested by GI disorders are determined by empirical methods known in the art.

[0038] The concentration of the active agents in the composition will depend on absorption, inactivation, excretion rates of the active compound, synergistic and/or additive effects, the dosage schedule, and amount administered as well as other factors known to those of skill in the art. Generally, the dosages and concentrations will be lower, typically at least about or at 5 to 10% lower but up to about or at 15, 20, 25, 30, 35, 40, 50, 90 or 95% lower than the amount of tapinarof and/or the at least one additional active agent the same active agents in the developed or marketed single drug currently being developed or used for the treatment of GI disorders. The dosage and regimen of administration may be determined by dose finding studies, as known in the art.

[0039] Exemplary dosages, strengths and concentrations of tapinarof in the tapinarof combination compositions administered topically, can be typically in the range of from about or at 0.1%, 0.25%, 0.5%, 1%, 2%, 5%, 10%, 15% or 20% w/w tapinarof.

[0040] The frequency of administration can be determined empirically. Exemplary frequencies

are once daily, twice daily, four times daily, weekly, bi-weekly or monthly.

[0041] In an exemplary regimen of administration, each daily treatment includes the rectal administration to a subject in need thereof of 1-4 enemas daily, wherein each enema comprises 5g tapinarof (5-20g tapinarof daily, see Examples 1-4), thus amounting to daily administration of up to 20g tapinarof.

[0042] Typical administration frequencies of the topical combination compositions of this invention are once daily to four times daily.

[0043] Dosage frequencies can be gradually attenuated over time and maintained at a steady dose suitable for long-term - six months, 1 year, 5 years, 10 years or more, up to lifelong administration to control the symptoms of the GI disorder. For example, dosage administration can begin at from four times a day, twice a day, to once a day, to two times a week, to once a week, to once every two weeks or less frequent than once every two weeks.

Kits

[0044] Kits are provided, containing the dosage forms and composition of this invention, optionally including instructions for administration. The dosage forms include, for example, the compositions as provided herein. Additionally, provided herein are kits containing the above-described compositions and optionally instructions for administration by the rectal route.

[0045] The compositions provided herein can be packaged as articles of manufacture containing packaging material, a composition provided herein, and a label that indicates that the composition is meant for treating GI disorders, and is formulated for rectal delivery.

[0046] The articles of manufacture provided herein contain packaging materials. Packaging materials for use in packaging pharmaceutical products are well known to those of skill in the art. Examples of pharmaceutical packaging materials include, but are not limited to enemas, suppositories, bottles, tubes, containers, application syringes and any packaging material suitable for a selected formulation and intended mode of administration and treatment.

Embodiments

[0047] In some embodiments, there is provided a rectal composition comprising from about 0.1% w/w to about 20.0% w/w tapinarof and a carrier suitable for rectal administration.

[0048] In some other embodiments, there is provided a rectal composition comprising from about 0.1% w/w to about 20.0% w/w tapinarof and a carrier suitable for rectal administration, wherein

further comprising from about 0.01% w/w to about 20.0% w/w at least one additional active agent.

[0049]In some embodiments, the at least one additional active agent is selected from an anti-inflammatory, an immune system suppressor, an antibiotic, a local anesthetic and combinations thereof. In some other embodiments, the at least one additional active agent is selected from a corticosteroid, mesalamine, balsalazide, olsalazine, diclofenac, azathioprine, mercaptopurine, cyclosporine, methotrexate, ciprofloxacin, metronidazole, lidocaine, pramoxine and combinations thereof.

[0050] In some embodiments, there is provided a rectal composition comprising from about 0.1% w/w to about 20.0% w/w tapinarof and from about 0.25% w/w to about 20.0% w/w mesalamine.

[0051] In some other embodiments, there is provided a rectal composition comprising from about 0.1% w/w to about 20.0% w/w tapinarof, from about 0.25% w/w to about 20.0% w/w mesalamine and from about 0.25% w/w to about 2.0% w/w pramoxine.

[0052] In some embodiments, there is provided a rectal composition comprising from about 0.1% w/w to about 20.0% w/w tapinarof and from about 0.01% w/w to about 2.0% w/w budesonide.

[0053] In some other embodiments, there is provided a rectal composition comprising from about 0.1% w/w to about 20.0% w/w tapinarof, at least one additional active agent and further comprising a vasoconstrictor compound selected from phenylephrine, oxymetazoline, brimonidine, a NOS inhibitor, tetrahydrozoline, pseudoephedrine and combinations thereof.

[0054] According to some embodiments, there is provided a dosage form comprising a composition of this invention, wherein the composition is formulated in a dosage form selected from a rectal suppository, an enema, a cream, a lotion, a gel, an ointment, an emulsion, a solution, a suspension, an elixir, a tincture, a paste, a foam, an aerosol, a spray and an application syringe.

[0055] According to some other embodiments, there is provided a method of treatment, prevention or alleviation of an anal, rectal or distal GI disorder by rectal administration to a subject in need thereof a therapeutically effective amount of a composition of this invention, comprising from about 0.1% w/w to about 20.0% w/w tapinarof and optionally from about 0.01% w/w to about 20.0% w/w at least one additional active agent selected from an anti-inflammatory, an immune system suppressor, an antibiotic, a local anesthetic and combinations thereof, wherein the daily amount of tapinarof in said composition rectally administered to a subject in need thereof in the treatment is from about 1mg to about 20g.

[0056] In some embodiments, there is provided the above method of treatment of anal, rectal or distal GI disorders of this invention, wherein said GI disorder is selected from ulcerative proctitis, distal ulcerative colitis, proctosigmoiditis, hemorrhoids, anal fissure, anal fistula, perianal infection, perianal abscess, perianal itching and combinations thereof.

[0057] In some other embodiments, said method of treatment comprises once daily, twice daily or four times daily rectal administration to a subject in need thereof a therapeutically effective amount of the composition of this invention.

[0058] According to some embodiments, there is provided the method of treatment of this invention, wherein tapinarof and the optional at least one additional active agent exhibit an additive or synergistic effect, thereby allowing to reduce the amounts of the active agents in the composition.

[0059] According to some other embodiments, there is provided a regimen of administration comprising once daily, twice daily or four times daily rectal administration to a subject in need thereof of one or more dosage form units of this invention, until remission or alleviation of the GI disorder symptoms. In an exemplary regimen of administration, each daily treatment includes the rectal administration to a subject in need thereof of 1-4 enemas daily, which amounts to 5-20g tapinarof daily.

[0060] In some embodiments, there is provided a kit comprising one or more dosage forms of this invention and instructions for use.

Definitions

[0061] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which the invention pertains. In case of conflict, the specification, including definitions, takes precedence. All patents, patent applications, published applications, articles, publications and other published materials referred to throughout the entire disclosure herein, unless noted otherwise, are incorporated by reference in their entirety.

[0062] As used herein, the indefinite articles "a" and "an" mean "at least one" or "one or more" unless the context clearly dictates otherwise.

[0063] As used herein, the term "treating" or" treatment" includes curing a condition, treating a condition, preventing a condition, treating symptoms of a condition, curing symptoms of a

condition, ameliorating symptoms of a condition, treating effects of a condition, ameliorating effects of a condition, and preventing results of a condition.

[0064] As used herein, the terms “pharmaceutically active agent” or “active agent” or “active pharmaceutical ingredient” or “API” are interchangeable and mean the ingredient is a pharmaceutical drug which is biological active and is regulatory approved or approvable as such.

[0065] The term “ingredient” refers to a pharmaceutically acceptable ingredient which is included or is amenable to be included in FDA’s Inactive Ingredient database (IIG). Inactive ingredients sometimes exhibit some therapeutic effects, although they are not drugs.

[0066]As used herein, a "pharmaceutical composition" refers to a composition comprising one or more active ingredients with other components such as pharmaceutically acceptable ingredients or excipients. The purpose of a pharmaceutical composition is to facilitate administration of an active ingredient to a subject.

[0067]Whenever a numerical range is indicated herein, it is meant to include any cited numeral (fractional or integral) within the indicated range. The phrases “ranging/ranges between” a first indicate number and a second indicate number and “ranging/ranges from” a first indicate number “to” a second indicate number are used herein interchangeably and are meant to include the first and second indicated numbers and all the fractional and integral numerals therebetween.

[0068] The dimensions and values disclosed herein are not to be understood as being strictly limited to the exact numerical values recited. Instead, unless otherwise specified, each such dosage/percentage is intended to mean both the recited value and a functionally equivalent range surrounding that value. For example, a percentage disclosed as “1%” is intended to mean “about 1%”.

[0069] As used herein, numerical ranges preceded by the term “about” should not be considered to be limited to the recited range. Rather, numerical ranges preceded by the term “about” should be understood to include a range accepted by those skilled in the art for any given element in formulations according to the present invention.

[0070] As used herein, when a numerical value is preceded by the term "about", the term "about" is intended to indicate +/-10%.

[0071] The terms "comprise", "comprising", "includes", "including", “having” and their conjugates mean "including but not limited to".

[0072] The term “consisting of” means “including and limited to”.

[0073] The term "consisting essentially of" means that the composition, method formulation may include additional ingredients, steps and/or parts, but only if the additional ingredients, steps and/or parts do not materially alter the basic and novel characteristics of the claimed composition, method or structure.

[0074] As used herein the term "method" refers to manners, means, techniques and procedures for accomplishing a given task including, but not limited to, those manners, means, techniques and procedures either known to, or readily developed from known manners, means, techniques and procedures by practitioners of the chemical, pharmacological, biological, biochemical and medical arts.

[0075] It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable sub-combination or as suitable in any other described embodiment of the invention. Certain features described in the context of various embodiments are not to be considered essential features of those embodiments, unless the embodiment is inoperative without those elements.

[0076] Various embodiments and aspects of the present invention as delineated hereinabove and as claimed in the claims section below find experimental support in the following examples.

EXAMPLES

[0077] Reference is now made to the following examples, which together with the above descriptions illustrate some embodiments of the invention in a non-limiting fashion.

[0078] Generally, the nomenclature used herein and the laboratory procedures utilized in the present invention include chemical, molecular and biochemical, techniques. Such techniques are thoroughly explained in the literature. General references are provided throughout this document. The procedures therein are believed to be well known in the art and are provided for the convenience of the reader. All the information contained therein is incorporated herein by reference.

EXAMPLE 1

Preparation of a Tapinarof Rectal Suspension Enema

[0079] Each rectal suspension enema unit (60 mL) contains 5 grams of tapinarof.

[0080] The disposable unit includes an applicator tip protected by a polyethylene cover and lubricated with USP white petrolatum. The unit has a one-way valve to prevent back-flow of the dispensed product.

[0081] The tapinarof enema composition consists of:

5 g tapinarof having less than 1 micron particle size,

0.5-2.0g carbomer 934P,

0.2-0.5g edetate disodium,

0.2-0.5g potassium acetate,

0.5-1.0g potassium metabisulfite,

0.5-1.0g xanthan gum,

0.2-0.5g sodium benzoate.

Make up to 60 mL with purified water

Fill the tapinarof composition in a 60 mL enema.

Each daily treatment includes the rectal administration to a subject in need thereof of 1-4 enemas daily (5-20g tapinarof daily).

EXAMPLE 2

Preparation of a Tapinarof-Mesalamine Rectal Composition Enema

[0082]Each rectal suspension enema unit (60 mL) contains 5 grams of tapinarof and 3 grams of mesalamine. The disposable unit includes an applicator tip protected by a polyethylene cover and lubricated with USP white petrolatum. The unit has a one-way valve to prevent back-flow of the dispensed product.

[0083]The tapinarof-mesalamine enema composition consists of:

5 g tapinarof (8.3% w/w) having less than 1 micron particle size

3 g mesalamine (5.0% w/w) having less than 1 micron particle size,

0.5-2.0g carbomer 934P,

0.2-0.5g edetate disodium,

0.2-0.5g potassium acetate,

0.5-1.0g potassium metabisulfite,

0.5-1.0g xanthan gum,

0.2-0.5g sodium benzoate.

Make up to 60 mL with purified water

Fill the tapinarof-mesalamine composition in a 60 mL enema.

[0084]Each daily treatment includes the rectal administration to a subject in need thereof of 1-4 enemas daily (5-20g tapinarof and 3-12g mesalamine daily).

EXAMPLE 3

Preparation of a Tapinarof-Budesonide Rectal Enema Composition

[0085]Each rectal suspension enema unit (60 mL) contains 5 grams of tapinarof and 15 mg budesonide. The disposable unit includes an applicator tip protected by a polyethylene cover and lubricated with USP white petrolatum. The unit has a one-way valve to prevent back-flow of the dispensed product.

[0086]The tapinarof-budesonide enema composition consists of:

5 g tapinarof (8.3% w/w) of less than 1 micron particle size,

0.015 g budesonide (0.025% w/w) of less than 1 micron particle size,

0.5-2.0g carbomer 934P,

0.2-0.5g edetate disodium,

0.2-0.5g potassium acetate,

0.5-1.0g potassium metabisulfite,

0.5-1.0g xanthan gum,

0.2-0.5g sodium benzoate.

Make up to 60 mL with purified water

Fill the tapinarof-budesonide composition in a 60 mL enema.

[0087]Each daily treatment includes the rectal administration to a subject in need thereof of 1-4 enemas daily (5-20g tapinarof and 15-60 mg budesonide daily).

EXAMPLE 4

Preparation of a Tapinarof-Mesalamine-Pramoxine Rectal Composition (Enema)

[0088]Each rectal suspension enema unit (60 mL) contains 5 grams of tapinarof, 3 grams of mesalamine and 0.6 grams pramoxine. The disposable unit includes an applicator tip protected by a polyethylene cover and lubricated with USP white petrolatum. The unit has a one-way valve to prevent back-flow of the dispensed product.

[0089]The tapinarof-mesalamine-pramoxine enema composition consists of:

5 g tapinarof (8.3% w/w) having less than 1 micron particle size

3 g mesalamine (5.0% w/w) having less than 1 micron particle size,

0.6 g (1.0% w/w) pramoxine

0.5-2.0g carbomer 934P,

0.2-0.5g edetate disodium,

0.2-0.5g potassium acetate,

0.5-1.0g potassium metabisulfite,

0.5-1.0g xanthan gum,

0.2-0.5g sodium benzoate.

Make up to 60 mL with purified water

[0090]Fill the tapinarof-mesalamine-pramoxine composition in a 60 mL enema.

[0091]Each daily treatment includes the rectal administration to a subject in need thereof of 1-4 enemas daily (5-20g tapinarof, 3-12g mesalamine and 0.6-2.4g pramoxine daily).

CLAIMS

What is Claimed is:

1. A rectal composition comprising from about 0.1% w/w to about 20.0% w/w tapinarof and a carrier suitable for rectal administration.

2. The composition of claim 1, wherein further comprising from about 0.01% w/w to about 20.0% w/w at least one additional active agent.

3. The composition of claim 2, wherein the at least one additional active agent is selected from an anti-inflammatory, an immune system suppressor, an antibiotic, a local anesthetic and combinations thereof.

4. The composition of any one of claims 2 or 3, wherein the at least one additional active agent is selected from a corticosteroid, mesalamine, balsalazide, olsalazine, diclofenac, azathioprine, mercaptopurine, cyclosporine, methotrexate, ciprofloxacin, metronidazole, lidocaine, pramoxine and combinations thereof.

5. The composition of any one of claims 2-4, wherein comprising from about 0.1% w/w to about 20.0% w/w tapinarof and from about 0.25% w/w to about 20.0% w/w mesalamine.

6. The composition of any one of claims 2-4, wherein comprising from about 0.1% w/w to about 20.0% w/w tapinarof, from about 0.25% w/w to about 20.0% w/w mesalamine and from about 0.25% w/w to about 2.0% w/w pramoxine.

7. The composition of any one of claims 2-4, wherein comprising from about 0.1% w/w to about 20.0% w/w tapinarof and from about 0.01% w/w to about 2.0% w/w budesonide.

8. The composition of any one of claims 1-7, further comprising a vasoconstrictor selected from phenylephrine, oxymetazoline, brimonidine, a NOS inhibitor, tetrahydrozoline, pseudoephedrine and combinations thereof.

9. A dosage form comprising the composition of any one of claims 1-8, wherein the composition is formulated in a dosage form selected from a rectal suppository, an enema, a cream, a lotion, a gel, an ointment, an emulsion, a solution, a suspension, an elixir, a tincture, a paste, a foam, an aerosol, a spray and an application syringe.

10. A method of treatment, prevention or alleviation of an anal, rectal or distal GI disorder by rectal administration to a subject in need thereof a therapeutically effective amount of the composition of any one of claims 1-8, comprising from about 0.1% w/w to about 20.0% w/w tapinarof and optionally from about 0.01% w/w to about 20.0% w/w at least one additional active agent selected from an anti-inflammatory, an immune system suppressor, an antibiotic, a local anesthetic and combinations thereof, wherein the daily amount of tapinarof in said composition rectally administered to a subject in need thereof in the treatment is from about 1mg to about 20g.

11. The method of claim 10, wherein the anal, rectal or distal GI disorder is selected from ulcerative proctitis, distal ulcerative colitis, proctosigmoiditis, hemorrhoids, anal fissure, anal fistula, perianal infection, perianal abscess, perianal itching and combinations thereof.

12. The method of any one of claims 10-11, wherein the treatment comprises once daily, twice daily or four times daily rectal administration to a subject in need thereof a therapeutically effective amount of the composition of any one of claims 1-8.

13. The method of any one of claims 10-12, wherein tapinarof and the at least one additional active agent exhibit an additive or synergistic effect, thereby allowing to reduce the amounts of the active agents in the composition.

14. A regimen of administration comprising once daily, twice daily or four times daily rectal administration to a subject in need thereof of one or more dosage form units of claim 9 until remission or alleviation of the GI disorder symptoms.

15. A kit comprising one or more dosage forms of claim 9 and instructions for use.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL2020/050441

A. CLASSIFICATION OF SUBJECT MATTER
IPC (20200101) A61K 31/05, A61K 31/535, A61K 31/58, A61K 31/606, A61P 1/00, A61K 9/00
CPC (20130101) A61K 31/05, A61K 2300/00, A61K 31/535, A61K 31/58, A61K 31/606, A61P 1/00, A61K 9/0031
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)
IPC (20200101) A61K 31/05, A61K 31/535, A61K 31/58, A61K 31/606, A61P 1/00, A61K 9/00
CPC (20130101) A61K 31/05, A61K 2300/00, A61K 31/535, A61K 31/58, A61K 31/606, A61P 1/00, A61K 9/0031

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)
See extra sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2008255245 A1 (GENHUI CHEN, JOHN M. WEBSTER [CA]) 16 Oct 2008 (2008/10/16) abstract, para. [0010], [0020], [0072], [0095]-[0096], [0098], [0101], [0222], [0224]-[0225], figures 4 and 5	1,9-12,14
Y	abstract, para. [0010], [0020], [0072], [0095]-[0096], [0098], [0101], [0222], [0224]-[0225], figures 4 and 5	2-8,13,15
Y	NEAVIN D. R.: "The Role of the Aryl Hydrocarbon Receptor (AHR) in Immune and Inflammatory Diseases"; Int. J. Mol. Sci.; vol. 19, no. 12, pages 1-18; DOI: 10.3390/ijms19123851 03 Dec 2018 (2018/12/03) abstract, table 2, page 6-7 para. no. 5 and para. no. 7	1-15
Y	"Rowasa® (mesalamine) Rectal suspension enema"; retrieved from -https://web.archive.org/web/20170923165515/http://www.rxlist.com:80/rowasa-drug.htm 23 Sep 2017 (2017/09/23) the whole document	1-6,9-11,15

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

[X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"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
17 Jun 2020	17 Jun 2020

Name and mailing address of the ISA:
Israel Patent Office
Technology Park, Bldg.5, Malcha, Jerusalem, 9695101, Israel
Email address: pctoffice@justice.gov.il

Authorized officer
COHEN Keren

Telephone No. 972-73-3927150

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL2020/050441

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	"Budesonide rectal foam and enema"; retrieved from-https://web.archive.org/web/20171211193143/https://patient.info/medicine/budesonide-rectal-foam-and-enema-budenofalk-rectal-foam-entocort-enema 11 Dec 2017 (2017/12/11) the whole document	2,3,7,9-11,15
Y	"Pramoxine Rectal Aerosol Foam"; retrieved from- https://my.clevelandclinic.org/health/drugs/18111-hydrocortisone-pramoxine-rectal-aerosol-foam 28 Oct 2018 (2018/10/28) the whole document	2-4,6,9-11,15
Y	"PREPARATION H® HEMORRHOIDAL SUPPOSITORIES"; retrieved from- https://web.archive.org/web/20141103110522/https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=a23ded81-78ba-c199-a8f0-aaf360b216ff&type=display 03 Nov 2014 (2014/11/03) the whole document	2,3,8-11,15

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IL2020/050441

Patent document cited search report	Publication date	Patent family member(s)	Publication Date
US 2008255245 A1	16 Oct 2008	US 2008255245 A1	16 Oct 2008
		AT 444960 T	15 Oct 2009
		AU 2133001 A	18 Jun 2001
		AU 780700 B2	14 Apr 2005
		AU 2003271470 A1	23 Apr 2004
		AU 2003271470 B2	18 Mar 2010
		CA 2393297 A1	14 Jun 2001
		CA 2393297 C	05 Oct 2010
		CA 2501663 A1	15 Apr 2004
		CN 1407978 A	02 Apr 2003
		CN 1319959 C	06 Jun 2007
		CN 1688535 A	26 Oct 2005
		CN 1688535 B	09 Nov 2011
		DE 60043120 D1	19 Nov 2009
		EP 1248774 A2	16 Oct 2002
		EP 1248774 B1	07 Oct 2009
		EP 1554236 A1	20 Jul 2005
		ES 2334635 T3	15 Mar 2010
		HK 1051691 A1	18 Oct 2007
		JP 2003516400 A	13 May 2003
		JP 4880847 B2	22 Feb 2012
		JP 2006508930 A	16 Mar 2006
		KR 20020070310 A	05 Sep 2002
		KR 100805907 B1	21 Feb 2008
		KR 20050062581 A	23 Jun 2005
		US 2005059733 A1	17 Mar 2005
		US 7321050 B2	22 Jan 2008
		US 2008139666 A1	12 Jun 2008
		US 7868047 B2	11 Jan 2011
		US 2003171429 A1	11 Sep 2003

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IL2020/050441

Patent document cited search report	Publication date	Patent family member(s)	Publication Date
		US 2010094041 A1	15 Apr 2010
		WO 0142231 A2	14 Jun 2001
		WO 0142231 A3	01 Nov 2001
		WO 2004031117 A1	15 Apr 2004

International application No.
PCT/IL2020/050441

B. FIELDS SEARCHED:

* Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Databases consulted: NCBI, Esp@cenet, Google Patents, CAPLUS, BIOSIS, EMBASE, MEDLINE, PubMed, Google Scholar, DWPI
Search terms used: Tapinarof , 3,5-dihydroxy-4-isopropyl-trans-stilbene, 3,5-dihydroxy-4-isopropyl-stilbene, Benvitimod, GSK2894512, rectal administration, anal administration, suppository, enema, foam, cream , lotion, gel, NSAID, corticostoroid, amino salicylates, vasoconstrictors, antibiotics, mesalamine, mesalazine, balsalazide, budesonide, olsalazin, azathioprine, mercaptopurine, cyclosporine, methotrexate, ciprofloxacin, metronidazole, phenylephrine, lidocaine, pramoxine, GI diseases, gastrointestinal diseases,ulcerative proctitis, proctosigmoiditis, hemorrhoid, anal fissure, anal fistula, perianal infection, perinal abscess, perinal tching