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(54) Title: REDUCTION OF HAIR GROWTH

(57) Abstract: A topical composition for reduction in hair growth includes α-difluoromethylornithine and a dermatologically acceptable vehicle including urea.

# REDUCTION OF HAIR GROWTH

## BACKGROUND

The invention relates to reducing hair growth in mammals, particularly for cosmetic purposes.

A main function of mammalian hair is to provide environmental protection. However, that function has largely been lost in humans, in whom hair is kept or removed from various parts of the body essentially for cosmetic reasons. For example, it is generally preferred to have hair on the scalp but not on the face.

Various procedures have been employed to remove unwanted hair, including shaving, electrolysis, depilatory creams or lotions, waxing, plucking, and therapeutic antiandrogens. These conventional procedures generally have drawbacks associated with them. Shaving, for instance, can cause nicks and cuts, and can leave a perception of an increase in the rate of hair regrowth. Shaving also can leave an undesirable stubble. Electrolysis, on the other hand, can keep a treated area free of hair for prolonged periods of time, but can be expensive, painful, and sometimes leaves scarring. Depilatory creams, though very effective, typically are not recommended for frequent use due to their high irritancy potential. Waxing and plucking can cause pain, discomfort, and poor removal of short hair. Finally, antiandrogens -- which have been used to treat female hirsutism -- can have unwanted side effects.

It has previously been disclosed that the rate and character of hair growth can be altered by applying to the skin inhibitors of certain enzymes. These inhibitors include inhibitors of 5-alpha reductase, ornithine decarboxylase, S-adenosylmethionine decarboxylase, gamma-glutamyl transpeptidase, and transglutaminase. See, for example, Breuer et al., U.S. Pat. 4,885,289; Shander, U.S. Pat. 4,720,489; Ahluwalia, U.S. Pat. 5,095,007; Ahluwalia et al., U.S. Pat. 5,096,911; and Shander et al., U.S. Pat. 5,132,293.

α-Difluoromethylornithine (DFMO) is an irreversible inhibitor of ornithine decarboxylase (ODC), a rate-limiting enzyme in the *de novo* biosynthesis of putrescine, spermidine, and spermine. The role of these polyamines in cellular proliferation is not yet well understood. However, they seem to play a role in the synthesis and/or regulation of DNA, RNA and proteins. High levels of ODC and polyamines are found in cancer and other cell types that have high proliferation rates.

DFMO binds the ODC active site as a substrate. The bound DFMO is then decarboxylated and converted to a reactive intermediate that forms a covalent bond with the enzyme, thus preventing the natural substrate ornithine from binding to the enzyme. Cellular inhibition of ODC by DFMO causes a marked reduction in putrescine and spermidine and a variable reduction in spermine, depending on the length of treatment and the cell type. Generally, in order for DFMO to cause significant antiproliferative effects,

the inhibition of polyamine synthesis must be maintained by continuous inhibitory levels of DFMO because the half-life of ODC is about 30 min, one of the shortest of all known enzymes.

A skin preparation containing DFMO (sold under the name Vaniqa® by Bristol Myers Squibb), has recently been approved by the Food and Drug Administration (FDA) for the treatment of unwanted facial hair growth in women. Its topical administration in a cream based vehicle has been shown to reduce the rate of facial hair growth in women. Vaniqa® facial cream includes a racemic mixture of the "D-" and "L-" enantiomers of DFMO (i.e., D,L-DFMO) in the monohydrochloride form at a concentration of 13.9% by weight active (15%, as monohydrochloride monohydrate). The recommended treatment regimen for Vaniqa® is twice daily. The cream base vehicle in Vaniqa® is set out in Example 1 of U.S. 5,648,394, which is incorporated herein by reference. The cream base includes 2.5% ceteareth-20. Ceteareth-20 is a blend of two polyoxyethylene ethers of alkyl alcohols, having the chemical formulas $CH_3(CH_2)_{15}(OCH_2CH_2)_b$ OH and $CH_3$ $(CH_2)_{17}$ $(OCH_2CH_2)_b$ OH, where b has an average value of 20.

It generally takes about eight weeks of continuous treatment before the hair growth-inhibiting efficacy of Vaniqa® cream becomes apparent. Vaniqa® cream has been shown to decrease hair growth an average of 47%. In one study, clinical successes were observed in 35% of women treated with Vaniqa® cream. These women exhibited marked improvement or complete clearance of their condition as judged by physicians scoring a decrease in visibility of facial hair and a decrease in skin darkening caused by hair. Another 35% of the women tested experienced some improvement in their condition. However, there were some women who exhibited little or no response to treatment.

Accordingly, although Vaniqa® cream is an effective product, it would be even more effective if it provided an earlier onset of hair growth inhibition (i.e., exhibited efficacy earlier than eight weeks) and/or exhibited an increased clinical success rate (i.e., exhibited efficacy in a greater percentage of users). Such improved results cannot be obtained by simply increasing the concentration of D,L-DFMO in the cream vehicle. First, increasing the concentration of D,L-DFMO above about 14% can cause increased stinging of the skin and/or can leave a residue, making it aesthetically unacceptable. Second, it is difficult to formulate compositions with an active concentration above about 15% because significantly higher concentrations of D,L-DFMO are not adequately soluble in the vehicle or destabilize the emulsion.

Molecules that are identical to each other in chemical structural formula and yet are not superimposable upon each other are enantiomers. In terms of their physiochemical properties enantiomers differ only in their ability to rotate the plane of

plane-polarized light, and this property is frequently used in their designation. Those entiomers that rotate plane-polarized light to the right are termed dextrorotatory, indicated by either a (+) - or d- or D-before the name of the compound; those that rotate light to the left are termed laevorotatory indicated by a (-)- or 1- or L- prefix. A racemic mixture is indicated by either a (±) - or d,l- or D,L- prefix. By another convention (or nomenclature), the R,S or the sequence rule can be used to differentiate enantiomers based on their absolute configuration. Using this system the L-DFMO corresponds to the R-DFMO, and the D-DFMO corresponds to the S-DFMO. Enantiomers are physiochemically similar in that they have similar melting points, boiling points, relative solubility, and chemical reactivity in an achiral environment. A racemate is a composite of equal molar quantities of two enantiomeric species, often referred to as the DL-form. Individual enantiomers of chiral molecules may possess different pharmacological profiles, i.e., differences in pharmacokinetics, toxicity, efficacy, etc.

## SUMMARY

The present invention provides a method (typically a cosmetic method) of reducing human hair growth by applying to the skin, in an amount effective to reduce hair growth, a dermatologically acceptable topical composition including α-difluoromethylornithine (DFMO) and a dermatologically acceptable vehicle. The vehicle includes urea. The vehicle may include, for example, from 0.1% to 20% urea by weight, preferably from 1% to 12% urea by weight, more preferably from 2% to 10% urea by weight, and most preferably 4% to 10% urea by weight. Without being bound by any theory, it is believed that the urea enhances the water holding capacity of the skin, which in turn leads to enhanced DFMO absorption. The unwanted hair growth may be undesirable from a cosmetic standpoint or may result, for example, from a disease or an abnormal condition (e.g., hirsutism).

The preferred vehicle also optionally includes a polyoxyethylene ether having the chemical formula $R(OCH_2CH_2)_bOH$, where R is a saturated or unsaturated alkyl group including from 6 to 22 carbon atoms and b has an average value of from 2 to 200. Preferably the alkyl group includes from 8 to 20, more preferably from 10 to 18, carbon atoms and b is from 2 to 100, more preferably from 2 to 50, most preferably from 2 to 30. Without being bound by any theory, it is believed that the polyoxyethylene ether disrupts, solubilizes, and/or emulsifies the lipid component of the skin, leading to enhanced skin absorption of the DFMO. Preferred vehicles include from 0.1% to 20%, more preferably from 1% to 12%, and most preferably from 4% or 5% to 12%, of the polyoxyethylene ether by weight.

For purposes of this application, the vehicle includes all components of the composition except the DFMO. DFMO, as used herein, includes DFMO itself and

pharmaceutically acceptable salts thereof.

Preferably the DFMO will comprise at least about 70% or 80%, more preferably at least about 90%, most preferably at least about 95% of the L-DFMO. Ideally, the DFMO will be substantially optically pure L-DFMO. "Substantially optically pure" means that the DFMO comprises at least 98% L-DFMO. "Optically pure" L-DFMO means that the DFMO comprises essentially 100% L-DFMO.

Preferred compositions include about 0.1% to about 30%, preferably about 1% to about 20%, more preferably about 5% to about 15%, by weight of the DFMO.

The present invention also provides topical compositions including a dermatologically or cosmetically acceptable vehicle, urea, and difluoromethylornithine in an amount effective to reduce hair growth.

The above compositions generally have an enhanced efficacy relative to similar compositions having vehicles containing no urea. This enhanced efficacy can manifest itself, for example, in earlier onset of hair growth inhibiting activity, greater reduction of hair growth rate, and/or greater number of subjects demonstrating reduced hair growth.

Other features and advantages of the invention will be apparent from the description and from the claims.

## DETAILED DESCRIPTION

A preferred composition includes DFMO in an amount effective to reduce hair growth in a cosmetically and/or dermatologically acceptable vehicle including at least 1% by weight urea. A more preferred composition will also include at least 2% by weight of a polyoxyethylene ether having the chemical formula $R(OCH_2\ CH_2)_bOH$, where R is a saturated or unsaturated alkyl group including from 8 to 20 carbon atoms and b is from 2 to 100. The composition may be a solid, semi-solid, cream or liquid. The composition may be, for example, a cosmetic and dermatologic product in the form of an, for example, ointment, lotion, foam, cream, gel, or solution. The composition may also be in the form of a shaving preparation or an aftershave. The vehicle itself can be inert or it can possess cosmetic, physiological and/or pharmaceutical benefits of its own.

Preferred polyoxyethylene ethers include polyoxyethylene (2) stearyl ether (steareth-2) ($R=CH_3(CH_2)_{17}$, b=2), polyoxyethylene (2) oleyl ether (oleth-2) ($R=CH_3(CH_2)_7\ CHCH(CH_2)_8$, b=2), polyoxyethylene (4) lauryl ether (laureth-4) ($R=CH_3(CH_2)_{11}$, b=4), polyoxyethylene (23) lauryl ether (laureth-23) ($R=CH_3(CH_2)_{11}$, b=23), a mixture of polyoxyethylene (20) cetyl ether and polyoxyethylene (20) stearyl ether (ceteareth-20) ($R=CH_3(CH_2)_{15}$ and $CH_3(CH_2)_{17}$, b=20), and polyoxyethylene (20) stearyl ether (steareth-20) ($R=CH_3(CH_2)_{17}$, b=20).

The composition may include one or more other types of hair growth reducing agents, such as those described in U.S. Pat. 5,364,885 or U.S. Pat. 5,652,273.

The concentration of DFMO in the composition may be varied over a wide range up to a saturated solution, preferably from 0.1% to 30% by weight; the reduction of hair growth increases as the amount of DFMO applied increases per unit area of skin. The maximum amount effectively applied is limited only by the rate at which the DFMO penetrates the skin. The effective amounts may range, for example, from 10 to 3000 micrograms or more per square centimeter of skin.

Vehicles can be formulated with liquid or solid emollients, solvents, thickeners, humectants and/or powders. Emollients include, for example, stearyl alcohol, mink oil, cetyl alcohol, oleyl alcohol, isopropyl laurate, polyethylene glycol, olive oil, petroleum jelly, palmitic acid, oleic acid, and myristyl myristate. Solvents include, for example, water, ethyl alcohol, isopropanol, acetone, diethylene glycol, ethylene glycol, dimethyl sulfoxide, and dimethyl formamide.

Optically pure L-DFMO can be prepared by known methods. See, for example, U.S. Pat. 4,309,442, Gao et al., Ann. Pharm. Fr. 52(4):184-203 (1994); Gao et al., Ann. Pharm. Fr. 52(5):248-59 (1994); and Jacques et al., Tetrahedron Letters, 48:4617 (1971), all of which are incorporated by reference herein.

The following are examples of compositions.

EXAMPLES 1-4

Examples of DFMO formulations containing urea with or without a polyoxyethylene ether.

| Ingredient | Example - 1 | Example - 2 | Example - 3 | Example - 4 |
|---|---|---|---|---|
| | Percent (wt/wt) | Percent (wt/wt) | Percent (wt/wt) | Percent (wt/wt) |
| Water | q.s. | q.s. | q.s. | q.s. |
| Glyceryl Stearate1[1] | 4.16 | 4.24 | 3.94 | 4.24 |
| PEG-100 Stearate[1] | 4.01 | 4.09 | 3.80 | 4.09 |
| Cetearyl Alcohol[2] | 2.99 | 3.05 | 2.84 | 3.05 |
| Ceteareth-20[2] | 2.45 | 2.50 | 2.33 | 2.50 |
| Mineral Oil | 2.18 | 2.22 | 2.06 | 2.22 |
| Stearyl Alcohol | 1.64 | 1.67 | 1.55 | 1.67 |
| Dimethicone | 0.55 | 0.56 | 0.52 | 0.56 |
| Preservative[3] | 0.4 - 0.78 | 0.4 - 0.78 | 0.4 - 0.78 | 0.4 - 0.78 |
| Urea | 2-5 | 2-5 | 2-5 | 2-5 |
| Polyoxyethylene ether[4] | -------- | -------- | 5 | 5 |
| Vehicle total | 100% | 100% | 100% | 100% |
| | | | | |

| Ingredient | Example - 1 | Example - 2 | Example - 3 | Example - 4 |
|---|---|---|---|---|
| | Percent (wt/wt) | Percent (wt/wt) | Percent (wt/wt) | Percent (wt/wt) |
| DFMO[5] | 1 - 15% | 1 - 15% | 1 - 15% | 1 - 15% |

1. Available as a blend, for example Cithrol GMS A/S ES0743 from Croda Chemical Company (UK)
2. Available as a blend, for example Cosmowax EM5483 from Croda Chemical Company (UK)
3. Preservative: combination of phenoxyethanol and methyl -, ethyl -, propyl - and butyl - parabens. The preservative is available as premixed blend or as individual ingredients. The preservative could include all of these components or could contain only phenoxyethanol with one or more of the listed parabens.
4. The polyoxyethylene ether may be selected from: ceteareth-20, ceteth-20, steareth-20, oleth-2, steareth-2, laureth-23, or laureth-4, with ceteareth-20 being more preferred.
5. The active drug component DFMO is added at final levels of 1 to 15% to either the pre-emulsified (cream or lotion) vehicle in Examples 1 - 4, or is dissolved first in the water component and then the remaining ingredients are added to form a stable emulsion. After the DFMO addition, the concentrations of other ingredients in the vehicle are accordingly reduced. Preferably the DFMO is substantially optically pure L-DFMO.

## EXAMPLE 5

A composition contains up to 15% by weight DFMO in a vehicle containing water 61.2%, ethanol 14.4%, urea 5.0%, steareth-20 5.0%, propylene glycol 4.5%, dipropylene glycol 4.5%, benzyl alcohol 3.6%, and propylene carbonate 1.8%. In place of steareth-20, there can be substituted oleth-2, steareth-2, ceteth-20, ceteareth-20, laureth-23, or laureth-4.

## EXAMPLE 6

Any one or more of the previous examples in combination with one or more of the penetration enhancers selected from: terpenes (e.g., 3-hydroxy-3,7,11-trimethyl-1,6,10-dodecatriene or nerolidol), propan-2-ol, cis-fatty acids (oleic acid, palmitoleic acid), acetone, laurocapram, dimethyl sulfoxide, 2-pyrrolidone, oleyl alcohol, cholesterol, myristic acid isopropyl ester, and propylene glycol. A penetration enhancer may be added at a concentration of, for example, 0.10% to 20% by weight.

The composition should be topically applied to a selected area of the body from which it is desired to reduce hair growth. For example, the composition can be applied to the face, particularly to the beard area of the face, i.e., the cheek, neck, upper lip, or chin. The composition also may be used as an adjunct to other methods of hair removal including shaving, waxing, mechanical epilation, chemical depilation, electrolysis and laser-assisted hair removal.

The composition can also be applied to the legs, arms, torso or armpits. The composition is particularly suitable for reducing the growth of unwanted hair in women, particularly unwanted facial hair, for example, on the upper lip or chin. The composition should be applied once or twice a day, or even more frequently, to achieve a perceived reduction in hair growth. Perception of reduced hair growth can occur as

early as 24 hours or 48 hours (for instance, between normal shaving intervals) following use or can take up, to, for example, three months. Reduction in hair growth is demonstrated when, for example, the rate of hair growth is slowed, the need for removal is reduced, the subject perceives less hair on the treated site, or quantitatively, when the weight of hair removed (i.e., hair mass) is reduced (quantitatively), subjects perceive a reduction, for example, in facial hair, or subjects are less concerned or bothered about their unwanted hair (e.g., facial hair).

SKIN PENETRATION ASSAY

An in vitro diffusion assay for vehicles was established based on that reported by Franz, Curr. Prol. Dermat. 7:58-68 (1978). Dorsal skin from Golden Syrian hamsters was clipped with electric clippers, trimmed to the appropriate size and placed in a diffusion chamber. The receptor fluid consisted of phosphate buffered saline, an isotonic solution for maintaining cell viability and 0.1% sodium azide, a preservative, and was placed in the lower chamber of the diffusion apparatus such that the level of the fluid was equal to the skin. After equilibration at 37°C for at least 30 minutes, 10 µl or 20 µl of $^{14}$C-DFMO (0.5 to 1.0 T Ci per diffusion chamber) in a test or control formulation was added to the surface of the skin and gently spread over the entire surface with a glass stirring rod. Penetration of DFMO was assessed by periodically removing an aliquot (400 TL) throughout the course of the experiment, and quantitating using liquid scintillation.

This assay was conducted on the vehicle described in Example 1 (with 2% urea). The vehicle not including urea was used as the control. The urea increased DFMO skin penetration over 2-fold after two hours and about 1.5-fold after 24 hours.

The assay also was conducted on the vehicle described in Example 3 (with 2% urea) where the polyoxyethylene ether was selected from either laureth-4, steareth-20 or ceteareth-20. The vehicle not including the urea or the further quantity of polyoxyethylene ether was used as the control. For these vehicles, DFMO penetration was enhanced about 2-fold or more after six hours.

The assay was also conducted on the vehicle described in Example 5. The vehicle not including the urea or the steareth-20 was used as the control. The DFMO penetration was increased by about 3-fold after two or six hours.

Other embodiments are within the scope of the following claims.

## CLAIMS

1. A method of reducing human hair growth, comprising selecting an area of skin from which reduced hair growth is desired, and applying to the area of skin, in an amount effective to reduce hair growth, a composition including α-difluoromethylornithine and a dermatologically acceptable vehicle comprising urea.

2. The method of claim 1, wherein the vehicle includes from 0.1% to 20% by weight urea.

3. The method of claim 1, wherein the vehicle includes from 1% to 12% by weight urea.

4. The method of claim 1, wherein the vehicle includes from 2% to 10% by weight urea.

5. The method of claim 2, wherein the vehicle includes at least 4% by weight urea.

6. The method of claim 1, wherein the vehicle further comprises a polyoxyethylene ether having the chemical formula $R(OCH_2CH_2)_b$ OH, where R is a saturated or unsaturated alkyl group including from 6 to 22 carbon atoms and b is from 2 to 200.

7. The method of claim 6, wherein the vehicle includes from 0.1% to 20% by weight of the polyoxyethylene ether.

8. The method of claim 7, wherein the vehicle includes at least 2% by weight of the polyoxyethylene ether.

9. The method of claim 7, wherein the vehicle includes at least 4% by weight of the polyoxyethylene ether.

10. The method of claim 9, wherein the vehicle includes from 1% to 12% by weight urea.

11. The method of claim 10, wherein the vehicle includes at least 2% by weight urea.

12. The method of claim 10, wherein the vehicle includes at least 4% by weight urea.

13. The method of claim 12, wherein the composition includes from 5% to 20% by weight α-difluoromethylornithine.

14. The method of claim 13, wherein the α-difluoromethylornithine is substantially optically pure L-α-difluoromethylornithine.

15. The method of claim 6, wherein R includes from 10 to 20 carbon atoms.

16. The method of claim 6, wherein b has an average value of from 2 to 50.

17. The method of claim 6, wherein the polyoxyethylene ether is selected

from the group consisting of steareth-2, oleth-2, laureth-4, laureth-23, ceteth-20, steareth-20, ceteareth-20, and mixtures of two or more of thesepolyoxyethylene ether.

18. The method of claim 6, wherein the polyoxyethylene ether is ceteareth-20.

19. The method of claim 1, wherein the α-difluoromethylornithine comprises at least about 80% of L-α-difluoromethylornithine.

20. The method of claim 1, wherein the α-difluoromethylornithine comprises at least about 95% of L-α-difluoromethylornithine.

21. The method of claim 1, wherein the area of skin is on the face.

22. A composition for topical application to the skin, comprising αdifluoromethylornithine in an amount effective to reduce hair growth and a dermatologically acceptable vehicle comprising urea.

23. The composition of claim 22, wherein the vehicle includes from 1% to 12% by weight urea.

24. The composition of claim 23, wherein the vehicle includes at least 2% by weight urea.

25. The composition of claim 23, wherein the vehicle includes at least 4% by weight urea.

26. The composition of claim 22, wherein the vehicle further comprises a polyoxyethylene ether having the chemical formula $R(OCH_2CH_2)_b$ OH, where R is a saturated or unsaturated alkyl group including from 6 to 22 carbon atoms and b is from 2 to 200.

27. The composition of claim 26, wherein the vehicle includes from 2% to 20% by weight of the polyoxyethylene ether.

28. The composition of claim 27, wherein the vehicle includes at least 4% by weight of the polyoxyethylene ether.

29. The composition of claim 26, wherein the vehicle includes from 2% to 12% by weight urea.

30. The composition of claim 29, wherein the vehicle includes at least 4% by weight of the urea and the composition includes from 5% to 15% by weight substantially optically pure L-α-difluoromethylornithine.

31. The composition of claim 26, wherein R includes from 10 to 20 carbon atoms and b is from 2 to 50.

32. The composition of claim 26, wherein the polyoxyethylene ether is selected from the group consisting of steareth-2, oleth-2, laureth-4, laureth-23, ceteth-20, steareth-20, ceteareth-20, and mixtures of two or more of thesepolyoxyethylene ether.

33. The composition of claim 26, wherein the polyoxyethylene ether is ceteareth-20.

34. The composition of claim 22, wherein the α-difluoromethylornithine ornithine comprises at least about 80% L-α-difluoromethylornithine.

35. The composition of claim 22, wherein the α-difluoromethylornithine comprises at least about 95% L-α-difluoromethylornithine.

36. The method according to any one of claims 1 to 21, wherein said applying of said inhibitor has a cosmetic effect.

37. The composition according to any one of claims 22 to 35, which is a cosmetic composition.

38. The use of urea for the manufacture of a medicament comprising a α-difluoromethylornithine reducing human hair growth.

39. The use according to claim 38, wherein said medicament includes a dermatologically acceptable vehicle.

40. The use according to claim 39, wherein the medicament is as defined in any one of claims 2 to 20.

41. A method of producing a composition for inhibiting mammalian hair growth, which comprises admixing urea with α-difluoromethylornithine, said α-difluoromethylornithine being in an amount effective to reduce hair growth, and with a non-toxic, dermatologically acceptable vehicle or carrier.

42. A method according to claim 41, wherein a cosmetic composition is produced.

43. A method according to claim 41, wherein said composition is as defined in any one of claims 23 to 35.

# INTERNATIONAL SEARCH REPORT

Int ional Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/198 A61K31/17 A61K7/00 A61P17/00

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 7 A61Q A61K

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 practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 00 50002 A (GILLETTE CO ;HENRY JAMES P (US); AHLUWALIA GURPREET S (US))<br>31 August 2000 (2000-08-31)<br>page 2, line 17-22<br>page 1, line 20-26<br>page 4, line 7-15,29-31<br>example 2<br>--- | 1-43 |
| X | WO 01 54654 A (GILLETTE CO ;AHLUWALIA GURPREET S (US); STYCZYNSKI PETER (US))<br>2 August 2001 (2001-08-02)<br>page 2, line 11-21<br>page 4, line 14-20<br>page 3, line 23-32<br>example 4<br>---<br>-/-- | 1-43 |

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

[X] Patent family members are listed in annex.

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# INTERNATIONAL SEARCH REPORT

national application No.
PCT/US 02/24963

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

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

Although claims 1-21 and 36 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

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

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

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

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

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