EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent: 06.03.1996 Bulletin 1996/10

(21) Application number: 91913987.3

(22) Date of filing: 29.07.1991

(51) Int. Cl. 6: A61K 31/565, A61K 7/06 // (A61K31/565, 31:505)

(86) International application number: PCT/US91/05170

(87) International publication number: WO 92/02225 (20.02.1992 Gazette 1992/05)

(54) STIMULATION OF HAIR GROWTH WITH POTASSIUM CHANNEL OPENERS AND 5-ALPHA-REDUCTASE INHIBITORS

STIMULIERUNG DES HAARWUCHSES MIT KALIUMCHANNELÖFFNERN UND 5-ALPHA-REDUKTASE-INHIBITOREN

STIMULATION DE LA CROISSANCE CAPILLAIRE AU MOYEN D'AGENTS D'OUVERTURE DES CANAUX DE POTASSIUM ET D'INHIBITEURS DE 5-ALPHA-REDUCTASE

(84) Designated Contracting States: AT BE CH DE DK ES FR GB GR IT LI LU NL SE

(30) Priority: 10.08.1990 US 565777

(43) Date of publication of application: 26.05.1993 Bulletin 1993/21

(73) Proprietor: THE UPJOHN COMPANY
Kalamazoo, Michigan 49001 (US)

(72) Inventors:
• DIANI, Arthur, Robert
  Mattawan, MI 49071 (US)
• BUHL, Allen, Edwin
  Portage, MI 49002 (US)

• SCHOSTAREZ, Heinrich, Josef
  Portage, MI 49002 (US)

(74) Representative: Perry, Robert Edward et al
GILL JENNINGS & EVERY
Broadgate House
7 Eldon Street
London EC2M 7LH (GB)

(56) References cited:
WO-A-85/02543
WO-A-88/07361
WO-A-90/06100
DE-A- 3 615 396

Remarks:
The file contains technical information submitted after the application was filed and not included in this specification

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BACKGROUND OF THE INVENTION

The present invention relates to improved methods and compositions for promoting hair growth by the concomitant administration of a potassium channel opener such as minoxidil, cromakalim, pinacidil, or a compound selected from the classes of potassium channel openers such as s-triazine derivatives, benzopyran derivatives, pyridopyran derivatives and thiane-1-oxide compounds; and a 5α-reductase inhibitors, 17α-(N-tert-butylicarbamoyl)-4-aza-5-α-androst-1-en-3-one.

Since the discovery that minoxidil could promote hair growth and was useful in the treatment of androgenetic alopecia commonly known as "male pattern baldness" (US Patents 4,596,812; 4,139,619), alopecia areata, and balding in females, effort has been directed toward attempts to improve upon the sole use of a topical minoxidil composition by incorporating other active ingredients, for example the combinations of minoxidil/hydrocortisone and minoxidil/retinoids (DE 3827467-A).

Another approach has been to attempt to identify and quantify the biological mechanisms responsible for the initiating and controlling hair growth at the follicular level and intervening with therapeutic agents which stimulate hair growth. It is well known in the art that the onset of puberty results in changes in endocrine levels which result in, among other changes, the stimulation of facial hair growth (males), axillary hair growth (males and females), and pubic hair growth (males and females). One class of compounds implicated in these effects are the androgens.


Antiandrogen therapy offers a potential intervention to the treatment of male pattern baldness in men, and in women where it has been suggested that elevated androgen levels are responsible for the appearance of male pattern baldness. Rittmaster, R. S., Loriaux, D. L., Ann. Intern. Med., 106, 95 (1987). This class of compounds, the antiandrogens, have been subdivided into two major categories, the androgen receptor blockers and the 5α-reductase inhibitors. Androgen receptor blockers interfere with the binding of androgens, testosterone and dihydrotestosterone (DHT), to their receptors, while 5α-reductase inhibitors prevent the conversion of testosterone into DHT. The clinical use of androgen blockers, such as cyproterone acetate, in men is complicated with systemic effects on normal sexual function. This is not the case in women, where these agents are utilized. Burke, B. M., Cunliff, W.J., Br. J. Dermatol., 112, 124 (1985); Dawber, R. P. R., Sonnex, T., Ralfs, I., Br. J. Dermatol., Suppl. 107, 20 (1982). The other class of antiandrogens are the 5α-reductase inhibitors. These compounds block action of 5α-reductase and thus reduce the level of DHT in the peripheral tissue. Rittmaster, R. S., Stoner, E., Thompson, D. L., Nance, D., Lasserter, K. C., J. Androl., 10, 259 (1989); Brooks, J. R., Berman, C., Prima, R. L., Reynolds, G. F., Rasmusson, G. H., Steroids, 47, 1 (1986). Rittmaster, R. S., Uno, H., Povar, M.L., J. Clin. Endocrinol. Metab., 65, 188 (1987) have shown that topical treatment of peridental stump mast macaque monkeys with the 5α-reductase inhibitor 4-MA prevented the progression of baldness normally observed in this species. Similar studies in humans have not been reported.

The coupling of hair growth stimulation with potassium channel activation has been inferred from literature reports of several vasodilators, minoxidil (through its metabolite minoxidil sulfate), pinacidil, and diazoxide, which cause varying degrees of hypertrichosis upon oral administration. Zins, G.R., Clin. Dermatol., 6, 132 (1988); Goldberg, M.R., J. Cardiovasc. Pharmacol., 12(Suppl. 2), S41 (1988); Okun, R., Russell, R.P., Wilson, W.R., Arch. Intern. Med., 112, 886 (1963). It is also known in the art that topical minoxidil is an effective treatment for androgenetic alopecia. The mechanism by which these compounds, minoxidil (through its metabolite minoxidil sulfate), pinacidil, and diazoxide, dilate vascular smooth muscle has been reported to be via the opening (activation) of potassium channels. Robertson, D. W., Steinberg, M. J., J. Med. Chem., 33, 1529 (1990). Thus potassium channel openers are useful in the treatment of androgenetic alopecia.

The surprising and unexpected result, and the subject of this invention, is the synergistic effect observed when both 17α-(N-tert-butylicarbamoyl)-4-aza-5-α-androst-1-en-3-one and minoxidil, a potassium channel opener, are utilized to stimulate or promote hair growth in a statistically significant fashion when compared to each drug alone.
INFORMATION DISCLOSURE STATEMENT

Topical minoxidil has been shown to be an effective treatment for male pattern baldness as described in US Patents 4,596,812 and 4,139,619. The utilization of 17β-(N-tert-butylcarbamoyl)-4-aza-5-α-androst-1-en-3-one for the treatment of androgenetic alopecia has been disclosed in European Patent Application 285 382 A2. The use of combinations of androgen receptor blocking agent (antiandrogen) and 5α-reductase inhibitors (not 17β-(N-tert-butylcarbamoyl)-4-aza-5-α-androst-1-en-3-one) has been disclosed in US Patent 4,684,635. The combination of minoxidil and an androgen receptor blocking agent for the treatment of male pattern baldness has also been disclosed in Patent Applications DE 3615-396-A and WO 8700-427-A. The combination of minoxidil and a 5α-reductase inhibitor for the treatment of male pattern baldness has also been disclosed in Japanese Patent Application JA 1305-017-A.

SUMMARY OF THE INVENTION

In one aspect, the subject invention is directed toward an improved method for promoting hair growth in mammals comprising the administration of a potassium channel opener in an effective amount and the administration of 17β-(N-tert-butylcarbamoyl)-4-aza-5-α-androst-1-en-3-one in an effective amount whereby hair growth is increased over the sole administration of the potassium channel opener. The routes of administration for either component can be by any of various means, preferably orally, topically or any combination of the two. More preferably and conveniently, the two components are applied together topically.

The potassium channel opener can be administered topically in an amount of from about 0.01 to about 20 percent by weight, or orally in an amount of from 0.01 to 50 mg/kg body weight. The 17β-(N-tert-butylcarbamoyl)-4-aza-5-α-androst-1-en-3-one can be administered topically in an amount of from 0.01 to 10 percent by weight of composition or administered orally in an amount of from 0.01 to 10 mg/kg body weight. The potassium channel opener and/or 17β-(N-tert-butylcarbamoyl)-4-aza-5-α-androst-1-en-3-one is generally administered in a pharmaceutical carrier adapted for oral administration or in a pharmaceutical acceptable carrier adapted for topical application.

Preferably, the potassium channel opener and 17β-(N-tert-butylcarbamoyl)-4-aza-5-α-androst-1-en-3-one are combined into a pharmaceutical carrier adapted for topical application. The potassium channel opener can be routinely applied to an area of treatment concomitant with the administration of 17β-(N-tert-butylcarbamoyl)-4-aza-5-α-androst-1-en-3-one.

The potassium channel opener is minoxidil, cromakalim, pinacidil, or a compound selected from the chemical classes of triazinines, thiename-1-oxides, benzopyrans, pyridinopyrans and derivatives thereof or a pharmaceutically acceptable salt thereof.

In another aspect, the subject invention is directed toward a pharmaceutical composition comprising an effective amount of a potassium channel opener, an effective amount of 17β-(N-tert-butylcarbamoyl)-4-aza-5-α-androst-1-en-3-one and a pharmaceutical carrier adapted for topical application. The pharmaceutical carrier can be petrolatum, lanolin, propylene glycol, N-methyl-2-pyrrolidinone, polyethylene glycol, oleyl alcohol, ethyl alcohol or mixtures thereof.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a method for promoting hair growth which means to increase normal hair growth or restore hair growth in mammals, including humans, suffering from hair growth disorders such as alopecia or male pattern baldness. The promotion or restoration of hair growth has been discovered to be significantly enhanced by the concomitant administration of a potassium channel opener (activators); and a 5α-reductase inhibitor, 17β-(N-tert-butylcarbamoyl)-4-aza-5-α-androst-1-en-3-one.

Typical examples of "potassium channel openers" or "potassium channel opener vasodilators" as contemplated by the subject invention are minoxidil, cromakalim, pinacidil, and those compounds selected from the chemical classes of triazinines, benzopyran, pyridinopyran and thiane-1-oxides their derivatives and pharmaceutically acceptable salts.

Minoxidil is chemically, 6-aminol-1,2-dihydro-2-hydroxy-2-imino-4-piperidinopyrimidine and analogs thereof. The preparation of these compounds are described in U.S. Patents 3,382,247, 3,461,461 and 3,644,364 and J.M. McCall, et al J. Org. Chem., 40, 3304 (1975). Related compounds are sulfophyridiminum, pyridinium, and triazinum which are described in U.S. Patent 4,287,338 herein incorporated by reference. Hereinafter, the term "minoxidil" means any of the various forms of 6-aminol-1,2-dihydro-2-hydroxy-2-imino-4-piperidinopyrimidine, derivatives and analogs thereof. Minoxidil is distributed by The Upjohn Company, Kalamazoo, MI.

Cromakalim is chemically, [35]trans) 3,4-dihydro-3-hydroxy-2,2-dimethyl-4-[2-oxo-1-pyrrolidinyl]-2H-1-benzopyran-6-carbonitrile, a molecular weight of 286.33 g. and a melting point of 224.5-225.5°C. Cromakalim is distributed by SmithKline Consumer Products, Philadelphia, PA.

Pinacidil is chemically, N-cyano-N'-4-pyrindinyl-N"-(1,2,2-trimethylpropyl)-guanidine monohydrate, a molecular weight of 263.34 g. and a melting point of 110-116°C. The preparation of pinacidil is described in US Patent 4,057,636 and German Patent 2,557,438 and is distributed by Eli Lilly and Company, Indianapolis, IN.
s-Triazine compounds or 2,6-diamino-4-substituted-s-triazine-1-oxides are described in U.S. Patent 3,270,014 assigned to The Upjohn Company, Kalamazoo, MI. Specific examples of these compounds include: N4-hexyl-2,4,6-triamino-1,3,5-triazine-1-oxide; N4-butyl-2,4,6-triamino-1,3,5-triazine-1-oxide; N4-pentyl-2,4,6-triamino-1,3,5-triazine-1-oxide; 4-(N,N-dipropyl)-2,6-diamino-1,3,5-triazine-1-oxide; 4-(N,N-dibutyl)-2,6-diamino-1,3,5-triazine-1-oxide; 4-(1-pyrrolidinyl)-2,6-diamino-1,3,5-triazine-1-oxide; 4-(N,N-dimethylaminomethyl)-2,6-diamino-1,3,5-triazine-1-oxide; and N4-ethyl-2,4,6-triamino-1,3,5-triazine-1-oxide.

Thiane-1-oxide compounds are described in U.S. Patent 4,568,682 assigned to Rhone-Poulenc Sante, Courbevoie, France. An example of such a compound contemplated by the subject invention is N-methyl-2-(pyridin-3-yl)tetrahydrothiophen-2-carbothioamide-1-oxide.


Pharmacologically acceptable salts of the potassium channel openers are for example acid addition salts which may be chosen from the following: acetate, adipate, alginic, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanecarboxylic, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, pircate, pivalate, propionate, succinate, tartrate, thiochinate, tosylate, and undecanoate.

Pharmacologically acceptable cationic salts of the potassium channel openers include: pharmacologically acceptable metal cations, ammonium, amine cations, or quaternary ammonium cations. Especially preferred metal cations are those derived from the alkali metals, e.g., lithium, sodium, and potassium, and from the alkaline earth metals, magnesium and calcium, although cationic forms of other metals, e.g., aluminum, zinc, and iron are also within the scope of this invention. Pharmacologically acceptable amine cations are those derived from primary, secondary, and tertiary amines.

The second essential, active ingredient of the subject invention is the compound 17β-(N-tert-butylcarbamoyl)-4-aza-5α-androst-1-en-3-one, (hereinafter referred to as "TBCAA") which has a molecular weight of 372.56. This compound is a 5α-reductase inhibitor and is described in European Patent Application 89302807.8, Publication No. 0285352, published 5 October 1988, assigned to Merck & Co., Inc., Rahway, NJ. This publication discloses various analogs of TBCAA all of which are disclosed to be active as testosterone 5α-reductase inhibitors and thus are useful for the treatment of androgenic alopecia, including male pattern alopecia. The preferred administration of TBCAA is topical. TBCAA can be administered by any of various routes as well as can be the potassium channel opener.

Administration routes for the two components of the subject invention can be topically, orally, parenterally or rectally. Typically, TBCAA is administered either topically with the potassium channel opener or orally while the potassium channel opener is applied topically. Preferably and most conveniently, the administration route would be to compound TBCAA with a potassium channel opener in a pharmaceutical, topical vehicle.

Typically, the potassium channel opener and optionally the 17β-(N-tert-butylcarbamoyl)-4-aza-5α-androst-1-en-3-one compound are applied to the skin region where hair growth is desired with a pharmaceutical carrier. More preferably, the pharmaceutical carrier is adopted for topical application such as those pharmaceutical forms which can be applied externally by direct contact with the surface to be treated.

Conventional pharmaceutical forms for this purpose include ointments, waxes, gels, lotions, pastes, jellies, sprays, aerosols, and the like in aqueous or nonaqueous formulations. The term "ointment" embraces formulations (including creams) having oleaginous, absorption, water-soluble and emulsion-type bases, e.g., petrolatum, lanolin, polyethylene glycols, N-methyl-2-pyrrolidinone, oleyl alcohol as well as mixtures of these.

Preparation of minoxidil topical compositions are disclosed in U.S. Patents 4,139,619 and 4,596,812, both herein incorporated by reference, as examples of how to prepare topical compositions for any of the potassium channel openers and/or the 17β-(N-tert-butylcarbamoyl)-4-aza-5α-androst-1-en-3-one.

Additionally, the potassium channel openers and/or the 17β-(N-tert-butylcarbamoyl)-4-aza-5α-androst-1-en-3-one compound can be admixed with other compounds for the treatment of hair growth. Such compounds which can be included in the overall composition or treatment are various combinations of the potassium channel openers, vasocostrictors such as betamethasone dipropionate, corticosteroids such as hydrocortisone, scopolamine, and antiandrogens such as cyoctol, and cyroterone acetate.

Typically, a potassium channel opener is used in an effective amount that is an amount sufficient to promote hair growth or treat hair growth disorders such that hair growth is increased or produced. The potassium channel opener is added in an amount of from 0.001 to 10, preferably, 0.01 to 5 percent by weight of the composition.
The 17\beta-(N-tert-butylcarbamoyl)-4-aza-5-\(\alpha\)-androsten-1-en-3-one compound is used in an effective amount, that is, an amount sufficient to promote hair growth or treat hair growth disorders such that hair growth is increased or produced over that which would be increased or produced by the administration of a potassium channel opener alone. The testosterone 5\(\alpha\)-reductase inhibitor, TBCAA, is added in an amount of from 0.0001 to 10, preferably, 0.001 to 5 percent by weight of the composition.

In a topical application, the compound or formulated composition can be applied to the area to be treated, in mammals such as the scalp in humans, by spraying, dabbing or swabbing. Other less specific methods can be employed provided the active ingredient(s) are delivered to the region of a hair follicle. Preferably, the compound or formulated composition is periodically applied to the treatment area on a routine basis prior to, during and subsequent to hair growth. Generally, the routine treatment would be to apply the compound or formulated composition at least daily, preferably twice daily although more frequent applications can be used.

The percentage by weight of the active ingredients, potassium channel opener and 17\beta-(N-tert-butylcarbamoyl)-4-aza-5-\(\alpha\)-androsten-1-en-3-one compound herein utilized ranges from an effective amount which is an amount sufficient to increase normal hair growth or treat various forms of alopecia whereby the hair growth is significantly more than if either of the compounds were solely administered. In topical preparations the pharmaceutical carrier for topical applications constitutes a major amount of the preparation. Typically, the active ingredient is in a range of from about 0.01 to about 10 percent total weight of the topical composition, preferably 0.1 to 5 percent total weight.

Experimentation:

The following protocol was utilized with the stump tail macaque monkey to demonstrate the synergistic affect of minoxidil and 17\beta-(N-tert-butylcarbamoyl)-4-aza-5-\(\alpha\)-androsten-1-en-3-one ("TBCAA") for promoting hair growth.

Twenty-one male stump tail macaque (Macaca speciosa) monkeys were assigned to vehicle control and drug treated groups on the basis of baseline hair weight data. This assignment procedure was necessary to insure that the average baseline hair growth for each control and experimental group was comparable. The control and drug treatment groups were as follows:

1. Topical 50:30:20 vehicle (N=6)
2. Oral TBCAA and topical 50:30:20 vehicle (N=5)
3. Oral TBCAA and topical 100mM minoxidil (N=5)
4. Topical 100mM minoxidil (N=5).

The vehicle consisted of 50% propylene glycol, 30% ethanol, and 20% water. The 100mM concentration of topical minoxidil was formulated in this vehicle. TBCAA was prepared as an oral dose of 0.5mg per monkey (interanimal weight range of 9.5-15.5 kg). Immediately prior to the dosing phase of the study, hair was removed from a 1 inch square area (identified by four tattoos) in the center of the balding scalp. This hair collection was the baseline hair growth determination prior to the beginning of treatment. Approximately 250\(\mu\)L of vehicle or 100mM minoxidil (prepared in vehicle) were topically administered to the tattooed area of the scalp. For the groups which received combined topical and oral dosing, 0.5 mg/monkey TBCAA was ingested by the monkeys at the same time as the topical dose was administered. The monkeys were dosed once per day, seven days per week for twenty weeks.

At four week intervals throughout the dosing phase of the study, each monkey was shaved and the hair was collected and weighed. The body weight data (at baseline and during assay) were analyzed by the nonparametric Wilcoxon rank-sum test. Differences were significant at \(p < 0.05\). The hair weight data (mean \pm SEM) at each 4 week collection for vehicle and treatment groups were expressed as the change from baseline. Statistical analysis (ANOVA) was performed on the ranks of the data to show overall differences among groups at each 4 week collection with \(p < 0.10\) marginally significant, \(p < 0.05\) significant, and \(p < 0.01\) highly significant.

Results:

The data reported in Tables I and II were obtained after 12 weeks of dosing, Tables III and IV after 16 weeks of dosing and in Tables V and VI after 20 weeks of dosing. They show that the combination of TBCAA and minoxidil is statistically superior in promoting hair growth, in this model, than the constituent agents alone.
After twelve weeks:

**TABLE I**

<table>
<thead>
<tr>
<th>Group</th>
<th>Hair Growth (mg)</th>
<th>p vs Vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBCAA</td>
<td>+1.4 ± 2.5</td>
<td>0.44</td>
</tr>
<tr>
<td>MINOXIDIL</td>
<td>+2.6 ± 1.0</td>
<td>0.20</td>
</tr>
<tr>
<td>MINOXIDIL + TBCAA</td>
<td>+7.6 ± 1.6</td>
<td>0.002</td>
</tr>
<tr>
<td>Vehicle</td>
<td>-0.3 ± 1.0</td>
<td>-</td>
</tr>
</tbody>
</table>

* Cumulative change in hair weight from baseline.

**TABLE II**

<table>
<thead>
<tr>
<th>Group</th>
<th>Hair Growth (mg)</th>
<th>p vs TBCAA/Minoxidil</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBCAA</td>
<td>+1.4 ± 2.5</td>
<td>0.02</td>
</tr>
<tr>
<td>MINOXIDIL</td>
<td>+2.6 ± 1.0</td>
<td>0.05</td>
</tr>
<tr>
<td>MINOXIDIL + TBCAA</td>
<td>+7.6 ± 1.6</td>
<td>-</td>
</tr>
<tr>
<td>Vehicle</td>
<td>-0.3 ± 1.0</td>
<td>0.002</td>
</tr>
</tbody>
</table>

* Cumulative change in hair weight from baseline.

After sixteen weeks:

**TABLE III**

<table>
<thead>
<tr>
<th>Group</th>
<th>Hair Growth (mg)</th>
<th>p vs Vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBCAA</td>
<td>+2.7 ± 2.3</td>
<td>0.09</td>
</tr>
<tr>
<td>MINOXIDIL</td>
<td>+3.1 ± 1.0</td>
<td>0.06</td>
</tr>
<tr>
<td>MINOXIDIL + TBCAA</td>
<td>+10.9 ± 1.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Vehicle</td>
<td>-1.0 ± 1.0</td>
<td>-</td>
</tr>
</tbody>
</table>

* Cumulative change in hair weight from baseline.

**TABLE IV**

<table>
<thead>
<tr>
<th>Group</th>
<th>Hair Growth (mg)</th>
<th>p vs TBCAA/Minoxidil</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBCAA</td>
<td>+2.7 ± 2.3</td>
<td>0.002</td>
</tr>
<tr>
<td>MINOXIDIL</td>
<td>+3.1 ± 1.0</td>
<td>0.002</td>
</tr>
<tr>
<td>MINOXIDIL + TBCAA</td>
<td>+10.9 ± 1.6</td>
<td>-</td>
</tr>
<tr>
<td>Vehicle</td>
<td>-1.0 ± 1.0</td>
<td>0.001</td>
</tr>
</tbody>
</table>

* Cumulative change in hair weight from baseline.
After twenty weeks:

### TABLE V

<table>
<thead>
<tr>
<th>Group</th>
<th>Hair Growth (mg)</th>
<th>p vs Vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBCAA</td>
<td>+2.2 ± 3.6</td>
<td>0.17</td>
</tr>
<tr>
<td>MINOXIDIL</td>
<td>+4.4 ± 1.0</td>
<td>0.03</td>
</tr>
<tr>
<td>MINOXIDIL + TBCAA</td>
<td>+13.5 ± 1.8</td>
<td>0.006</td>
</tr>
<tr>
<td>Vehicle</td>
<td>-1.3 ± 1.5</td>
<td>-</td>
</tr>
</tbody>
</table>

1 Cumulative change in hair weight from baseline.

### TABLE VI

<table>
<thead>
<tr>
<th>Group</th>
<th>Hair Growth (mg)</th>
<th>p vs TBCAA/Minoxidil</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBCAA</td>
<td>+2.2 ± 3.6</td>
<td>0.009</td>
</tr>
<tr>
<td>MINOXIDIL</td>
<td>+4.4 ± 1.0</td>
<td>0.009</td>
</tr>
<tr>
<td>MINOXIDIL + TBCAA</td>
<td>+13.5 ± 1.8</td>
<td>-</td>
</tr>
<tr>
<td>Vehicle</td>
<td>-1.3 ± 1.5</td>
<td>0.006</td>
</tr>
</tbody>
</table>

1 Cumulative change in hair weight from baseline.

The above data shows a statistically significant increase in the promotion of hair growth which is unexpected despite the known propensity of the potassium channel opener (minoxidil) and the testosterone 5α-reductase inhibitor (TBCAA) to individually affect hair growth. The combination of the two active ingredients therefore represents a significant advancement in the art of promoting, maintaining, or restoring hair growth in mammals.

**Claims**

1. A composition comprising a potassium channel opener and 17β-(N-tert-butylcarbamoyl)-4-aza-5-α-androst-1-en-3-one, as a combined product for concomitant administration for use in promoting hair growth in mammals whereby the hair growth is increased with respect to the sole administration of the potassium channel opener.

2. A composition according to claim 1, wherein the potassium channel opener is in a form adapted for topical administration.

3. A composition according to claim 2, which comprises 0.01 to 20% by weight of the potassium channel opener.

4. A composition according to any of claims 1 to 3, wherein the 17β-(N-tert-butylcarbamoyl)-4-aza-5-α-androst-1-en-3-one is in a form adapted for topical administration.

5. A composition according to claim 4, which comprises 0.001 to 10% by weight of the 17β-(N-tert-butylcarbamoyl)-4-aza-5-α-androst-1-en-3-one.

6. A composition according to any of claims 2 to 5, which comprises a pharmaceutical carrier selected from petrolatum, lanolin, propylene glycol, polyethylene glycol, oleyl alcohol, ethyl alcohol, N-methyl-2-pyrrolidinone and mixtures thereof.

7. A composition according to any of claims 1 to 3, wherein the 17β-(N-tert-butylcarbamoyl)-4-aza-5-α-androst-1-en-3-one is in a form adapted for oral administration.
8. A composition according to any preceding claim, wherein the potassium channel opener is selected from minoxidil, cromakalim, pinacidil and s-triazine, thiane-1-oxide, benzopyran or pyridinopyran derivatives, and pharmaceutically-acceptable salts thereof.

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9. A composition according to claim 8, wherein the potassium channel opener is minoxidil.

10. A composition according to any preceding claim, which comprises a compound selected from minoxidil, vasoconstrictors, corticosteroids, scopolamine, antiandrogens and mixtures thereof.

Patentansprüche

1. Zubereitung mit einem Kaliumkanalöffner und 17β-[(N-tert.-Butylicarbamoyl)]-4-aza-5-α-androsten-1-en-3-on als Kombinationsprodukt für eine gemeinsame Verabreichung zur Verwendung bei der Steigerung von Haarwachstum bei Säugetieren, wodurch das Haarwachstum gegenüber der alleinigen Verabreichung des Kaliumkanalöffners erhöht ist.

2. Zubereitung nach Anspruch 1, wobei der Kaliumkanalöffner in einer zur topischen Verabreichung geeigneten Form vorliegt.

3. Zubereitung nach Anspruch 2, umfassend 0,01 bis 20 Gew.-% des Kaliumkanalöffners.

4. Zubereitung nach einem der Ansprüche 1 bis 3, wobei das 17β-[(N-tert.-Butylicarbamoyl)]-4-aza-5-α-androsten-1-en-3-on in einer zur topischen Verabreichung geeigneten Form vorliegt.

5. Zubereitung nach Anspruch 4, umfassend 0,001 bis 10 Gew.-% des 17β-[(N-tert.-Butylicarbamoyl)]-4-aza-5-α-androsten-1-en-3-ons.


7. Zubereitung nach einem der Ansprüche 1 bis 5, wobei das 17β-[(N-tert.-Butylicarbamoyl)]-4-aza-5-α-androsten-1-en-3-on in einer zur oralen Verabreichung geeigneten Form vorliegt.


Revendications

1. Composition comprenant un agent d'ouverture des canaux potassium et de la 17β-[(N-terti-butylcarbamoyl)]-4-aza-5-α-androst-1-ène-3-one, sous forme d'un produit mixte pour administration concomitante, destiné à être utilisé dans la stimulation de la croissance capillaire chez des mammifères, la croissance capillaire étant ainsi accrue par rapport à la seule administration de l'agent d'ouverture des canaux potassium.

2. Composition suivant la revendication 1, dans laquelle l'agent d'ouverture des canaux potassium est sous une forme apte à l'administration topique.

3. Composition suivant la revendication 2, qui comprend 0,01 à 20 % en poids de l'agent d'ouverture des canaux potassium.

4. Composition suivant l'une quelconque des revendications 1 à 3, dans laquelle la 17β-[(N-terti-butylcarbamoyl)]-4-aza-5-α-androst-1-ène-3-one est sous une forme apte à l'administration topique.
5. Composition suivant la revendication 4, qui comprend 0,001 à 10 % en poids de la 17β-(N-tertio-butylcarbamoyl)-
4-aza-5-α-androst-1-ène-3-one.

6. Composition suivant l’une quelconque des revendications 2 à 5, qui comprend un support pharmaceutique choisi
entre la vaseline, la lanoline, le propylène-glycol, le polyéthylène-glycol, l’alcool oléyle, l’alcool éthyle, la N-
méthyl-2-pyrrolidinone et leurs mélanges.

7. Composition suivant l’une quelconque des revendications 1 à 3, dans laquelle la 17β-(N-tertio-butylcarbamoyl)-4-
aza-5-α-androst-1-ène-3-one est sous une forme apte à l’administration orale.

8. Composition suivant l’une quelconque des revendications précédentes, dans laquelle l’agent d’ouverture des canaux
potassium est choisi entre le minoxidil, le cromakalim, le pinacidil et la s-triazine, le thiane-1-oxyde, le benzopyranne
ou des dérivés de benzopyranne, et leurs sels pharmaceutiquement acceptables.

9. Composition suivant la revendication 8, dans laquelle l’agent d’ouverture des canaux potassium est le minoxidil.

10. Composition suivant l’une quelconque des revendications précédentes, qui comprend un composé choisi entre le
minoxidil, des vasoconstricteurs, des corticostéroïdes, la scopolamine, des anti-androgènes et leurs mélanges.