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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : A61K 7/06, 31/505, 31/57 A61K 31/46	A1	(11) International Publication Number: WO 90/06100 (43) International Publication Date: 14 June 1990 (14.06.90)
(21) International Application Number: PCT/US89/04775 (22) International Filing Date: 30 October 1989 (30.10.89) (30) Priority data: 279,366 2 December 1988 (02.12.88) US (60) Parent Application or Grant (63) Related by Continuation US 279,366 (CON) Filed on 2 December 1988 (02.12.88) (71) Applicant (for all designated States except US): THE UPJOHN COMPANY [US/US]; 301 Henrietta Street, Kalamazoo, MI 49001 (US). (72) Inventor; and (75) Inventor/Applicant (for US only) : FIEDLER, Virginia, C. [US/US]; 6635 Sunburst, Portage, MI 49002 (US).		(74) Agent: CORNEGLIO, Donald, L.; Patent Law Department, The Upjohn Company, Kalamazoo, MI 49001 (US). (81) Designated States: AT (European patent), AU, BE (European patent), CH (European patent), DE (European patent), DK, FI, FR (European patent), GB (European patent), HU, IT (European patent), JP, KR, LU (European patent), NL (European patent), NO, SE (European patent), SU, US. Published <i>With international search report.</i>
(54) Title: MINOXIDIL AND VASOCONSTRICTOR COMPOSITIONS FOR TREATING ALOPECIA (57) Abstract An improved composition and method for the promotion of hair growth or treatment of alopecia where the composition comprises at least 2.5 percent of minoxidil and a vasoconstrictor in an effective amount wherein hair growth is increased over the application of minoxidil alone. The composition can be present in a topical formulation using suitable pharmaceutical carriers. The method comprises the topical administration of the minoxidil and vasoconstrictor in an effective amount to stimulate hair growth.		

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MINOXIDIL AND VASOCONSTRICTOR COMPOSITIONS
FOR TREATING ALOPECIA

Background of the Invention

The present invention relates to an improved composition for
5 treating alopecia, including alopecia areata which can effect young
children. The improved composition is effective in the treatment of
alopecia which is generally defined as a baldness resulting from
common male pattern baldness or hair loss disorders which can occur
in females and young children. In the latter two situation, while
10 the disorder poses little threat to the individuals health, it can be
emotionally devastating. Therefore it is desirable to develop new
and improved methods for restoring hair growth.

The present invention comprises an application of minoxidil and
vasoconstrictors which is herein demonstrated to have superior hair
15 growth results over the application of minoxidil alone. Minoxidil
and its analogs are well known in the treatment of hair loss. For
example, minoxidil is available by prescription as ROGAINE® a
trademark of The Upjohn Company, Kalamazoo, Michigan. The prepara-
tion of minoxidil topical compounds for application to the scalp are
20 also disclosed in U.S. Patents 4,139,619 and 4,596,812.

Previously, the attempted use of a 2% solution of minoxidil and
betamethasone cream (a vasoconstrictor) was reported by the inventor
in Pediatric Dermatology, Vol. 4, No. 2, pages 136-158 (page 150)
(1987) entitled "Special Symposium: Alopecia Areata Symposium".
25 However, no effect was reported and the levels of minoxidil was low
as compared to the improved treatment and composition of the present
invention.

Information Disclosure

Topical compositions of minoxidil for the treatment of hair
30 growth, alopecia, are known as disclosed in U.S. Patents 4,139,619
and 4,596,812. Also, background information on various minoxidil
compounds and analogs is disclosed in U.S. Patents 3,382,247,
3,461,461, 3,644,364 and 4,287,338. Also, the use of a 2% solution
of minoxidil with betamethasone cream was reported in Pediatric
35 Dermatology, Vol. 4, No. 2, pages 136-158 (page 150) (1987) entitled
"Special Symposium: Alopecia Areata Symposium".

Summary of the Invention

In one aspect the subject invention is an improved composition

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for the promotion of hair growth or treatment of alopecia comprising minoxidil in an amount of at least 2.5 percent and a vasoconstrictor in an effective amount wherein hair growth is increased over the use of minoxidil alone. A vasoconstrictor is a corticosteroid or a
5 scopolamine, preferably
betamethasone dipropionate. The amount of a vasoconstrictor is from about 0.01 to about 1.0 percent, preferably about 0.01 to about 0.10 percent, more preferably 0.05 percent.

The composition can additionally include a pharmaceutical
10 carrier adapted for topical application.

In another aspect, the present invention is a method for treating or preventing alopecia comprising the topical administration to hair follicles of a composition comprising at least 2.5% minoxidil and a vasoconstrictor in an effective amount to treat or prevent
15 alopecia. The topical administration can be preformed by applying the minoxidil and vasoconstrictor either separately or simultaneously as a single topical application. In the method the composition is routinely applied to the hair follicles, preferably twice daily or daily.

20 Detailed Description of the Invention

The improved topical composition for the treatment of hair growth comprises minoxidil and a vasoconstrictor. The minoxidil portion is 6-amino-1,2-dihydro-hydroxy-2-imino-4-piperidinopyrimidine and analogs thereof. The preparation of these compounds are described
25 in U.S. Patents 3,382,247, 3,461,461 and 3,644,364 and J.M. McCall, et al., Journal of Organic Chemistry, 40, 3304 (1975) all of which are hereby incorporated by reference. Related compounds are sulfoxypyrimidinium, -pyridinium, and -triazinium which are described in U.S. Patent 4,287,338 herein incorporated by reference. Herein-
30 after, the term "minoxidil" means any of the various forms of 6-amino-1,2-dihydro-hydroxy-2-imino-4-piperidinopyrimidine, derivatives and analogs thereof.

Minoxidil is present in the composition in an amount of from about one to about five percent by weight ("percent"), preferably at
35 least two and a half to about five percent. Best results can be achieved when the minoxidil is present in an amount of about five percent; however, when treating children lesser amounts of minoxidil is employed to avoid any adverse reactions.

The vasoconstrictor portion of the composition provides enhanced action of the minoxidil and hair growth is significantly improved versus an application of only minoxidil.

Ideally, the vasoconstrictor is incorporated with minoxidil such
5 that they can both be applied in a single application. Alternatively, the vasoconstrictor and minoxidil can be applied separately to the treatment area without departing from the improved benefit of this invention. Therefore, the term "composition" and amounts of
10 either minoxidil and vasoconstrictor present therein are determined when both are present on the treatment area regardless of method of application.

Vasoconstrictors appropriate for applying or compounding with minoxidil comprise potent topical corticosteroids which can include a class of natural and synthetic compounds. Typically these steroids
15 are hormones secreted by the adrenal cortex and are noted for their vasoconstrictive actions. One preferred vasoconstrictor is betamethasone dipropionate. Other agents such as scopolamine which is a belladonna alkaloid and has vasoconstrictor activity can be used.

The vasoconstrictor is applied to the scalp or is present in the
20 composition from about 0.01 to about 1.0 percent, preferably from about 0.01 to about 0.10 percent, more preferably 0.05 percent.

The improved minoxidil composition is characterized by the presence of a vasoconstrictor as described above. Typically, the improved composition is a formulation of minoxidil and the vasocon-
25 strictor suitable for topical administration. The term "topical" means a composition of minoxidil and a composition of vasoconstrictor or both incorporated in a suitable pharmaceutical carrier which can be applied to the treatment site for local action.

Typical topical compositions include those pharmaceutical forms
30 in which can be applied externally by direct contact with the surface to be treated. Conventional pharmaceutical forms for this purpose include ointments, waxes, lotions, pastes, jellies, sprays, aerosols, and the like in aqueous or nonaqueous formulations. The term "ointment" embraces formulations (including creams) having oleagin-
35 ous, absorption, water-soluble and emulsion-type bases, e.g., petrolatum, lanolin, polyethylene glycols, as well as mixtures of these.

Preparation of minoxidil topical compositions are disclosed in

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U.S. Patents 4,139,619 and 4,596,812, both herein incorporated by reference. The preparation of topical compositions containing both minoxidil and a vasoconstrictor is the result of admixing the vasoconstrictor with the minoxidil topical composition.

5 The improved composition can be applied to the area to be treated, such as the scalp in humans, by spraying, dabbing or swabbing. Other less specific methods can be employed provided the active ingredients, minoxidil and vasoconstrictor, are delivered to the region of the hair follicle. Preferably, the composition is
10 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 minoxidil and vasoconstrictor at least daily, preferably twice daily. In some situations where the alopecia areata is in remission treatment can be discontinued.

15 Four patients with severe, treatment resistant alopecia areata were treated with one milliliter of a 2% topical minoxidil solution by applying it to their entire scalp. The patients also had their entire scalp treated with a 1 gram application of a vasoconstrictor, betamethasone dipropionate 0.05% cream. The vasoconstrictor in some
20 treatments was applied 30 minutes before and in some cases 30 minutes after the minoxidil treatment. All four patients exhibited cosmetically good hair growth and have maintained the regrowth with continued treatment. This program demonstrated the improved results of combining a vasoconstrictor with minoxidil.

25 In additional studies patients with alopecia areata are treated with 5% topical minoxidil solution and applications of betamethasone dipropionate 0.05% cream. The higher level of minoxidil and simultaneous application of a vasoconstrictor will provide good hair growth.

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CLAIMS

1. A composition for the promotion of hair growth comprising:
 - (a) minoxidil in an amount of at least 2.5 percent; and
 - (b) a vasoconstrictor in an effective amount wherein hair
- 5 growth is increased over the use of minoxidil alone.
2. The composition of claim 1 wherein said vasoconstrictor is a corticosteroid or a scopolamine.
- 10 3. The composition of claim 2 wherein said vasoconstrictor is betamethasone dipropionate.
4. The composition of claim 1 wherein the amount of a vasoconstrictor is from about 0.01 to about 1.0 percent.
- 15 5. The composition of claim 4 wherein the amount of a vasoconstrictor is from about 0.01 to about 0.10 percent.
6. The composition of claim 5 wherein the amount of a vasoconstrictor is 0.05 percent.
- 20 7. The composition of claim 1 which includes a pharmaceutical carrier adapted for topical application.
- 25 8. Use of a topically administered composition comprising at least 2.5% minoxidil and a vasoconstrictor in an effective amount wherein hair growth is increased over the use of minoxidil alone for the promotion of hair growth.
- 30 9. The use of claim 8 wherein said vasoconstrictor is corticosteroid or a scopolamine.
10. The use of claim 9 wherein said vasoconstrictor is betamethasone dipropionate.
- 35 11. The use of claim 8 wherein the amount of a vasoconstrictor is from about 1.0 to about 0.01 percent.

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12. The use of claim 8 which includes a pharmaceutical carrier adapted for topical application.

13. The use of claim 8 wherein said composition is routinely applied
5 to an area of treatment.

14. The use of claim 13 wherein said composition is applied daily or twice daily.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 89/04775

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC IPC ⁵ : A 61 K 7/06, 31/505, 31/57, 31/46																	
II. FIELDS SEARCHED Minimum Documentation Searched ⁷ <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 30%; border-bottom: 1px solid black; padding: 5px;">Classification System </td> <td style="border-bottom: 1px solid black; padding: 5px;">Classification Symbols</td> </tr> <tr> <td style="padding: 10px 5px 5px 5px;">IPC⁵</td> <td style="padding: 10px 5px 5px 5px;">A 61 K</td> </tr> </table> Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸			Classification System	Classification Symbols	IPC ⁵	A 61 K											
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III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹ <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 10%; border-bottom: 1px solid black; padding: 5px;">Category ⁹</th> <th style="width: 60%; border-bottom: 1px solid black; padding: 5px;">Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²</th> <th style="width: 30%; border-bottom: 1px solid black; padding: 5px;">Relevant to Claim No. ¹³</th> </tr> <tr> <td style="vertical-align: top; padding: 5px;">A</td> <td style="padding: 5px;">Pediatric Dermatology, vol. 4, no. 2, 1987, Blackwell Scientific Publ. Inc. N. Burton Esterly: "Alopecia Areata Symposium", pages 136-158, see page 150, paragraph 2 (cited in the application)</td> <td style="vertical-align: top; padding: 5px;">1-14</td> </tr> <tr> <td style="vertical-align: top; padding: 5px;">A</td> <td style="padding: 5px;">WO, A, 88/07361 (THE UPJOHN CO.) 6 October 1988, see the claims</td> <td style="vertical-align: top; padding: 5px;">1-14</td> </tr> <tr> <td style="vertical-align: top; padding: 5px;">A</td> <td style="padding: 5px;">FR, A, 2101044 (ORSYMONDE) 31 March 1972, see example 1</td> <td style="vertical-align: top; padding: 5px;">1-14</td> </tr> <tr> <td colspan="3" style="text-align: center; padding: 20px 0;">-----</td> </tr> </table>			Category ⁹	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³	A	Pediatric Dermatology, vol. 4, no. 2, 1987, Blackwell Scientific Publ. Inc. N. Burton Esterly: "Alopecia Areata Symposium", pages 136-158, see page 150, paragraph 2 (cited in the application)	1-14	A	WO, A, 88/07361 (THE UPJOHN CO.) 6 October 1988, see the claims	1-14	A	FR, A, 2101044 (ORSYMONDE) 31 March 1972, see example 1	1-14	-----		
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A	FR, A, 2101044 (ORSYMONDE) 31 March 1972, see example 1	1-14															

¹⁰ Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document 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 "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																	
IV. CERTIFICATION <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; border-bottom: 1px solid black; padding: 5px;">Date of the Actual Completion of the International Search</td> <td style="width: 50%; border-bottom: 1px solid black; padding: 5px;">Date of Mailing of this International Search Report</td> </tr> <tr> <td style="padding: 5px;">14th February 1990</td> <td style="padding: 5px;">22 MAR 1990</td> </tr> <tr> <td style="border-bottom: 1px solid black; padding: 5px;">International Searching Authority</td> <td style="border-bottom: 1px solid black; padding: 5px;">Signature of Authorized Officer</td> </tr> <tr> <td style="padding: 5px;">EUROPEAN PATENT OFFICE</td> <td style="padding: 5px;"> T.K. WILLIS </td> </tr> </table>			Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	14th February 1990	22 MAR 1990	International Searching Authority	Signature of Authorized Officer	EUROPEAN PATENT OFFICE	T.K. WILLIS							
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**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

US 8904775

SA 32196

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 06/03/90
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A- 8807361	06-10-88	AU-A- 1542288	02-11-88
FR-A- 2101044	31-03-72	None	