NEW TOPICAL PREPARATION FOR TREATMENT OF ALOPECIA

This invention relates to pharmaceutical compositions for treatment of alopecia comprising a compound of formula (I), in the form of the free base or acid addition salts thereof, in association with a pharmaceutical carrier adapted for topical application to mammalian skin. The compounds used have general formula (I), in which the R₂-substituted cyanoguanidyl radical is placed in the 3- or 4-position of the pyridine ring, and in which R₁ stands for a straight or branched, saturated or unsaturated, aliphatic hydrocarbon radical having from 1 to 8 carbon atoms, a cycloalkyl or cycloalkenyl radical having from 3 to 7 carbon atoms, or an aryl or an aralkyl radical. R₂ stands for hydrogen, halogen, hydroxy, lower alkyl or alkoxy radicals. The present compositions find applications both in the human and veterinary use.
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New topical preparation for treatment of alopecia.

This invention relates to pharmaceutical compositions for topical application comprising a compound of the formula I, in the form of the free base or acid addition salts thereof, in association with a pharmaceutical carrier adapted for topical application to mammalian skin.

Another aspect of the invention is a process for increasing the rate of terminal hair growth and a process for stimulating the conversion of vellus hair to growth as terminal hair.

The compounds used in the present composition and process are known as hypotensives, e.g. described in US patent Re. 31,244. They have the general formula I:

\[
\begin{array}{c}
  \text{R}_2 \\
  \text{N-CN} \\
  \text{NH-C-NH-R}_1
\end{array}
\]

in which the \( \text{R}_1 \)-substituted cyano-guanidyl radical is placed in the 3- or 4-position of the pyridine ring, and in which \( \text{R}_1 \) stands for a straight or branched, saturated or unsaturated, aliphatic hydrocarbon radical having from 1 to 8 carbon atoms, a cycloalkyl or cycloalkenyl radical having from 3 to 7 carbon atoms, or an aryl or an aralkyl radical. \( \text{R}_2 \) stands for hydrogen, halogen, hydroxy, lower alkyl or alkoxy radicals. The present invention comprises all stereoisomers of formula I as well as mixtures thereof.

In particular, the present composition and process use as active compound of formula I either N-tert-butyl-N"-cyano-N'-3-pyridylguanidine (in the following also designated P 1060) or N"-cyano-N-4-pyridyl-N'-1,2,2-trimethylpropylguanidine (in the following also designated pinacidil).

Alopecia (a partial or complete loss of hair) may result from genetic factors, aging, or from local or systemic disease. Male-pattern baldness is extremely common,
it is familial and requires the presence of androgens, but other etiological factors are unknown. Female-pattern alopeci
is not infrequent in women. It is ordinarily confined to thinning of hair in the frontal and the parietal regions. Complete baldness in any area is rare.

Alopecia is due to a deficiency of terminal hair which is the visual coloured hair. If the hair loss is due to atrophy or scarring, no regrowth can be expected. But in other cases, even where there is a noticeable absence of terminal hair, the skin of a seemingly bald person may contain the so-called vellus hair which is a very fine colourless hair, the presence of which needs microscopic determination. The vellus hair is a precursor to the terminal hair, and a regrowth may thus be promoted both by influencing the conversion of vellus hair to terminal hair and by stimulating the growth of the latter.

As alopecia is mainly a cosmetic problem, any therapy should never present risks which are unjustifiable. It has surprisingly turned out that the present compositions can be effectively used for the desired purpose. They find applications both in the human and veterinary use, the latter in particular being of economic importance in connection with animals raised for their pelts, e.g. mink. The present compositions can be used over the entire surface of the body for improving the pelt for commercial reasons, or they can be used partially to cure e.g. bald patches.

The pharmaceutical compositions contemplated by this invention include pharmaceutical compositions suited for topical application.

The term "topical" as employed herein relates to the use of a compound of the formula I, incorporated in a suitable pharmaceutical topical base in form of a solution and/or a suspension in which the active compound is suspended as a microfine powder. Accordingly, such topical compositions include those pharmaceutical forms in which the compound is applied externally by direct contact with the skin surface to be treated. Conventional pharmaceutical
forms for this purpose include ointments, lotions, pastes, jellies, sprays, aerosols, and the like. The term "ointment" embraces formulations (including creams) having oleaginous, absorption, water-soluble and emulsion-type bases, e.g. petrolatum, lanolin, polyethylene glycols, as well as mixtures of these.

The present compositions may advantageously further contain percutaneous penetration enhancers, such as N-methyl-2-pyrrolidone, azone, propylene glycol, and poly(oxyethylene)-poly(oxypropylene) co-polymers.

The percentage by weight of the compound of the formula I herein utilized ranges from about 0.1% to about 20.0% of the pharmaceutical preparation, preferably from about 0.5% to about 5% and in these preparations the aforesaid pharmaceutical carrier for topical application constitutes a major amount of the said preparation.

The following examples describe the manner and process of making and using the invention and set forth the best mode contemplated by the inventor of carrying out the invention but are not to be construed as limiting.

**Example 1**

**Topical ointment**

- P 1060: 20 g
- Paraffin, liquid: 200 g
- White soft paraffin to make: 1000 g

The fatty ingredients are melted at increased temperature, and the active substance P 1060 is incorporated by homogenizing. The ointment is cooled and filled into suitable containers.

**Example 2**

**Topical ointment**

- Pinacidil: 100 g
- Sorbitan sesquioleate: 50 g
- Paraffin, liquid: 100 g
- White soft paraffin to make: 1000 g

Preparation as described in Example 1.
Example 3

Topical (waterfree/watermiscible) ointment

P 1060 50 g
Polyethylene glycol 400 250 g
Polyethylene glycol 4000 700 g

The glycols are melted at increased temperature. The active substance P 1060 is incorporated. The preparation is cooled and filled into suitable containers.

Example 4

Topical cream

Pinacidil 50 g
Paraffin, liquid 100 g
White soft paraffin 50 g
Cetyl alcohol 100 g
Polyoxyethylene sorbitan monostearate 50 g
Methylparaben 2 g
Propylparaben 0.2 g
Glycerol 100 g
Water to make 1000 g

The fatty ingredients including the emulsifying agent are melted by increased temperature. At increased temperature the water phase including the active substance pinacidil and a solution of the preservative are mixed with the melted fatty phase. The cream is homogenized, cooled, and filled into suitable containers.

Example 5

Topical cream

P 1060 10 g
Cetostearyl alcohol 100 g
White soft paraffin 150 g
Liquid paraffin 50 g
Cetomacrogol 1000 20 g
Chlorocresol 1 g
Water to make 1000 g

Preparation as described in Example 4.
Example 6

Topical hydrogel

Pinacidil 50 g
Carbomer 10 g
Methylparaben 2 g
Propylparaben 0.2 g
Silicone oil 30 g
Triethanolamine 5 g
Water to make 1000 g

The preservatives are dissolved and mixed with the carbomer. A gel is formed by the addition of triethanolamine. Finally, pinacidil and silicone oil are added, and the gel is homogenized.

The gel is filled into suitable containers.

Example 7

Topical gel

P 1060 10 g
Liquid paraffin 20 g
Cetostearyl alcohol 20 g
Polyoxyethylene-2-stearylether 3 g
Polyoxyethylene-10-stearylether 7 g
Methylparaben 2 g
Propylparaben 0.2 g
Propylene glycol 100 g
Carbomer 10 g
Triethanolamine 5 g
Water to make 1000 g

The fatty ingredients including the emulsifying agent are melted at increased temperature. The water phase including a solution and/or a homogeneous suspension of the active substance P 1060, the preservatives, and the carbomer are mixed with the fatty phase.

The mixture is homogenized, gelled by the addition of the triethanolamine, and then filled into suitable containers.
6. **Example 8**

**Topical lotion**

P 1060 30 g
Propylene glycol 50 g
Isopropyl alcohol 850 g
Water to make 1000 g

The active substance is dissolved in the pharmaceutical base.

**Example 9**

**Topical lotion**

Pinacidil 50 g
Polyethylene glycol 4000 120 g
Myristyl-γ-picolinium chloride 0.2 g
Polyvinylpyrrolidone 1 g
Deionized water q.s. ad 1000 c.c.

The ingredients are dissolved in water and filled into containers.

The composition so prepared can be used in the topical treatment of baldness by application to the scalp daily.

**Example 10**

**Topical spray**

**Aerosol (foam)**

P 1060 10 g
Polawax A 31 40 g
Ethyl alcohol 600 g
Polyvinylpyrrolidone 30 g
Glycerol 10 g
Water 220 g
Dichlorodifluoromethane 40 g
Dichlorotetrafluoroethane 60 g

All ingredients are dissolved or suspended in ethyl alcohol and the water. The concentrate is filled into aerosol containers and the propellants are added.
7.

**Example 11**

**Topical Spray**

**Aerosol**

- Pinacidil 1.5 g
- Absolute alcohol 4.3 g
- Dichlorodifluoroethane 1.43 g
- Dichlorotetrafluoroethane 5.70 g

The pinacidil is suspended in the absolute alcohol. The suspension is chilled to about minus 30°C. To this is added the chilled mixture of dichlorodifluoromethane and dichlorotetrafluoroethane. 13 ml plastic-coated amber bottles are cold filled with 11.5 g each of the resulting solution and capped.

The compositions can be sprayed on the scalp daily to convert vellus hair to growth as terminal hair.

**Example 12**

**Dusting Powder**

- P 1060 10 g
- Magnesium stearate 5 g
- Silicone dioxide colloidal 10 g
- Lactose 478 g
- Maize starch 500 g

The powdered ingredients are mixed together.

**Example 13**

**Dusting Powder**

- P 1060 10 g
- Bentonite 100 g
- Talc q.s. 1000 g

The powdered ingredients are mixed together and dusted on the fur of minks for increasing the rate of hair growth.
WHAT WE CLAIM IS:

1. A topical composition for application to mammalian skin comprising an effective amount of a compound of formula I:

\[
\begin{array}{c}
\text{R}_2 \\
\text{N-CN} \\
\text{NH-C-NH-R}_1 \\
\end{array}
\]

in which the \( R_1 \)-substituted cyano-guanidyl radical is placed in the 3- or 4-position of the pyridine ring, and in which \( R_1 \) stands for a straight or branched, saturated or unsaturated, aliphatic hydrocarbon radical having from 1 to 8 carbon atoms, a cycloalkyl or cycloalkenyl radical having from 3 to 7 carbon atoms, or an aryl or an aralkyl radical, and \( R_2 \) stands for hydrogen, halogen, hydroxy, lower alkyl or alkoxy radicals; all stereoisomers thereof and mixtures of same, and the pharmaceutically acceptable acid addition salts thereof; in association with a topical pharmaceutical carrier selected from the group consisting of ointments, lotions, pastes, jellies, sprays, and aerosols.

2. The composition of claim 1 wherein the concentration of the compound is from about 0.1% to about 20% of the composition.

3. The composition of claim 1 wherein the compound is N-tert-butyl-N'-cyano-N'-3-pyridylguanidine or acid addition salts thereof.

4. The composition of claim 1 wherein the compound is N'-cyano-N-4-pyridyl-N'-1,2,2-trimethylpropylguanidine or acid addition salts thereof.

5. A process for increasing the rate of terminal hair growth in mammalian species comprising the application to mammalian skin at the locale of terminal hair of an effective amount of a compound of formula I:
in which the \( R_1 \)-substituted cyano-guanidyl radical is placed in the 3- or 4-position of the pyridine ring, and in which \( R_1 \) stands for a straight or branched, saturated or unsaturated, aliphatic hydrocarbon radical having from 1 to 8 carbon atoms, a cycloalkyl or cycloalkenyl radical having from 3 to 7 carbon atoms, or an aryl or an aralkyl radical, and \( R_2 \) stands for hydrogen, halogen, hydroxy, lower alkyl or alkoxy radicals; all stereoisomers thereof and mixtures of same, and the pharmaceutically acceptable acid addition salts thereof; in association with a topical pharmaceutical carrier.

6. The process of claim 5 wherein the concentration of the compound applied is from about 0.1% to about 20% of the composition.

7. The process of claim 5 wherein compound applied is N-tert-butyl-N'-cyano-N'-3-pyridylguanidine.

8. The process of claim 5 wherein compound applied is N'-cyano-N-4-pyridyl-N'-1,2,2-trimethylpropylguanidine.

9. A process for the conversion of vellus hair to growth as terminal hair comprising the application to mammalian skin at the locale of vellous hair of an effective amount of a compound of formula I:

\[
\begin{align*}
\text{N-CN} & \\
\text{NH-C-NH-R}_1 \\
\end{align*}
\]

in which the \( R_1 \)-substituted cyano-guanidyl radical is placed in the 3- or 4-position of the pyridine ring, and in which \( R_1 \) stands for a straight or branched, saturated or unsaturated, aliphatic hydrocarbon radical having from 1 to 8 carbon atoms, a cycloalkyl or cycloalkenyl radical
having from 3 to 7 carbon atoms, or an aryl or an aralkyl radical, and $R_2$ stands for hydrogen, halogen, hydroxy, lower alkyl or alkoxy radicals; all stereoisomers thereof and mixtures of same, and the pharmaceutically acceptable acid addition salts thereof; in association with a topical pharmaceutical carrier.

10. The process of claim 9 wherein the concentration of the compound applied is from about 0.1% to about 20% of the composition.

11. The process of claim 9 wherein the compound applied is N-tert-butyl-N'-cyano-N'-3-pyridylguanidine.

12. The process of claim 9 wherein the compound applied is N'-cyano-N-4-pyridyl-N'-1,2,2-trimethylpropylguanidine.

13. A topical composition for application for mammalian skin substantially as hereinbefore described in any one of the foregoing Examples.

14. The use of a compound of formula I

\[
\begin{align*}
\text{N} & \quad \text{N-CN} \\
\text{R}_2 & \quad \text{NH-C-NH-R}_1 \\
\end{align*}
\]

in which the $R_1$-substituted cyano-guanidyl radical is placed in the 3- or 4-position of the pyridine ring, and in which $R_1$ stands for a straight or branched, saturated or unsaturated, aliphatic hydrocarbon radical having from 1 to 8 carbon atoms, a cycloalkyl or cycloalkenyl radical having from 3 to 7 carbon atoms, or an aryl or an aralkyl radical, and $R_2$ stands for hydrogen, halogen, hydroxy, lower alkyl or alkoxy radicals; or of one or more stereoisomers thereof and/or one or more pharmaceutically acceptable acid addition salts thereof, for the manufacture of a composition for increasing the rate of terminal hair growth and/or stimulating the conversion of vellus hair to growth as terminal hair.
**INTERNATIONAL SEARCH REPORT**

**International Application No.** PCT/DK89/00006

### I. CLASSIFICATION OF SUBJECT MATTER

According to International Patent Classification (IPC) or to both National Classification and IPC:

- A 61 K 7/06, 31/44

### II. FIELDS SEARCHED

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Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched:

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### IV. CERTIFICATION

- **Date of the Actual Completion of the International Search:** 1989-04-20
- **Date of Mailing of this International Search Report:** 1989-04-27
- **International Searching Authority:** Swedish Patent Office

**Signature of Authorized Officer:**

Elisabeth Carlborg
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