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(71) Applicant *(for all designated States except US)*: SUNNIMEX LIMITED [GB/GB]; 66 Wigmore Street, London W1H 0HQ (GB).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: CAMPONOVO, Tiziano [IT/GB]; 66 Wigmore Street, London W1H 0HQ (GB).

(74) Agent: MINOJA, Fabrizio; Bianchetti Bracco Minoja S.r.l., Via Rossini, 8, I-20122 Milano (IT).

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(57) Abstract

The use of androst-5-ene-3β,17β-diol for the preparation of a medicament useful for the treatment of post-menopausal syndrome, for the treatment and prevention of osteoporosis, and inducing a decrease in the fat mass and an increase in the lean body mass, in menopausal and in both sexes in ageing.

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A MEDICAMENT USEFUL FOR THE TREATMENT OF POST-MENOPAUSAL SYNDROME AND OSTEOPOROSIS, AND FOR REDUCING FAT MASS AND INCREASING LEAN BODY MASS

Summary of invention

The present invention relates to the use of androst-5-ene-3β,17β-diol for the preparation of a medicament useful for the treatment of deficiencies of delta 5-androsten hormones. More particularly, androst-5-ene-3β,17β-diol is used in the treatment of post-menopausal syndrome, in the treatment and prevention of osteoporosis, and for inducing a decrease in fat mass and an increase in lean body mass.

Technological background

Androst-5-ene-3β,17β-diol is a 19 carbon atoms steroid produced physiologically by the human adrenal gland. The mean blood concentrations of this hormone are usually of about 4.5 nanomols (1.3 ng/ml) per litre. The blood values of this hormone decrease in menopausal woman (Cummings AC, et al.., J. Clin. Endocrinol. Metab. 54:1069-71, 1982), in obesity (Tchernof A, et al.. Metab. 44:517-19, 1995) and in ageing in both sexes (Parker LN. Academic. Press, New York, 615 pp, 1989). Androst-5-ene-3β,17β-diol is known to be used as an anabolic agent, i.e. it promotes an increase in muscle bulk.

Androstenediol is produced by the adrenal gland through hydroxylation of DHEA (dehydroepiandrosterone). The metabolic pathway of androstenediol is complex. This hormone is in part hydroxylated to both α and β androstenetriols. It should be stressed that DHEA,

androstenediol and its 7β-hydroxylated derivative are immune stimulators (Padgett DA. J. Immunol. 153:1544-52, 1994). This hormone is converted in peripheral tissues to androgens (mainly androstenedione and, to a lesser extent, testosterone) and estrogens (mainly estrone and, to a lesser extent, estradiol) by the action of the enzymes 17β dehydrogenase, 3β-dehydrogenase, 5-Δ 4 isomerase and 5α reductase and aromatase, mostly contained in the fat mass (Feher T. Endocrinologie. 80:173-180, 1982; Deslyper JP, et al.. J. Clin. Endocrinol. Metab. 61:564-570, 1985; Kilinger DW. Ann. NY Acad. Sci. 595:199-214, 1990).

The increase in fat mass and the reduction in the lean body mass is a metabolic alteration occurring with particular frequency in post-menopausal women (Aloia JF, et al.., Am. J. Obstet Gynecol. 172:896-900, 1995) and in both sexes in ageing.

During post-menopause woman spontaneously tends to gain weight as a consequence of an increase in fat mass, whereas her strength decreases as the muscle bulk is reduced (Aloia JF, et al... Am. J. Obstet Gynecol. 172:896-900, 1995; Morales AJ, et al... J. Clin. Endocrinol. Metab. 78:1360-67, 1994). These phenomena are associated to vasomotor disturbances, osteoporosis, changes in sexual behaviour, loss of libido, reduced sense of well-being, physiological and psychic fatigue. The traditional hormone replacement therapy, which has been used for a long time for the prevention and treatment of menopause, does not increases androstenediol blood levels nor modifies the fat mass/lean body mass ratio, which shifts towards fat

mass. The estrogen treatment often does not restore sexuality, libido and well-being.

Disclosure of the invention

It has now surprisingly been found that the administration of androst-5-ene-3β,17β-diol in the deficiencies of delta 5-androsten hormones reduces and eliminates menopausal disturbances, counteracts bone loss, reduces the fat mass, promoting an increase in the lean body mass until restoring a suitable balance thereof. Contrary to estrogens, androst-5-ene-3β,17β-diol does not stimulate the growth of endometrium; therefore it has not to be combined with progestins.

Therefore it is an object of the present invention the use of androst-5-ene-3β,17β-diol for the preparation of a medicament useful for the treatment of deficiencies of the above mentioned hormones.

More specifically, it is an object of the present invention the use of androst-5-ene-3β,17β-diol for the preparation of a medicament useful for the treatment of post-menopausal syndrome and osteoporosis, and for inducing a decrease in fat mass and an increase in lean body mass in menopausal women.

It is a further object of the present invention the use of androst-5-ene-3β,17β-diol for the preparation of a medicament useful for inducing a decrease in fat mass and an increase in lean body mass in ageing humans.

It is still a further object of the invention a pharmaceutical composition containing an effective amount of androst-5-ene-3β,17β-diol as active ingredient in admixture with pharmaceutically acceptable excipients and carriers, more particularly a composition suitable

for the oral administration, as well as a composition providing the administration of continuous doses of androst-5-ene-3β,17β-diol by the transdermal route.

Advantageously, the use of androst-5-ene-3β,17β-diol according to the present invention involves a very slight androgenic activity and the effective amounts of the active ingredient are very low.

Detailed disclosure of the invention

According to the present invention, the medicament containing androst-5-ene-3β,17β-diol is useful for the treatment of deficiencies of delta 5-androsten hormones, produced by the adrenal gland:

1) in the treatment of physio-pathological conditions characterized by asthenia, fatigue, loss of libido, decrease in strength and well-being, as occurring in post-menopause and, in both sexes, in ageing;
2) in the prevention and treatment of menopausal syndrome;
3) in the prevention and treatment of post-menopausal osteoporosis;
4) for restoring a suitable fat mass / lean body mass relationship, similar to that of the healthy human;
5) in the treatment of the conditions related to a decrease in androstenediol production by the adrenal gland, with a corresponding decrease in blood concentration, such as in chronic, infectious and psychic diseases characterized by hypercortisolism, any excessive action of which is counteracted by androst-5-ene-3β,17β-diol;
6) in the prevention of metabolic and psychophysical alterations occurring during menopause and ageing;

7) finally, in the treatment of men after the 50th year to modify climacteric symptoms, to reduce fat mass and to increase muscle strength.

Androst-5-ene-3β,17β-diol is a substantially harmless product present in the body as a natural component, so that it involves no toxicity problems.

Androst-5-ene-3β,17β-diol can be administered together with other active ingredients or directly combined therewith, in post-menopause and in ageing. In particular, it can be administered together with estrogens in the prevention and in the treatment of menopause symptoms and disturbances, without need for combining it with progestins.

According to the invention, suitable doses of androst-5-ene-3β,17β-diol range from 5 to 30 mg/day per os.

According to the present invention, the administration of androstenediol in post-menopausal women effectively counteracts menopausal symptoms and decreases fat mass, contrary to estrogens which do not affect it, thus suggesting a regulating activity of androstenediol on fatty tissue. This action is not likely to be exerted by dehydroepiandrosterone (DHEA), another C19 steroid precursor of androstenediol, having, like the latter, a protein anabolic action. In fact, the treatment of obese patients with DHEA does not seem to cause a loss of fat mass (Usiskin KS, et al.. Int. J. Obes. 14:457-463, 1990). Khaw KT, et al.. (Ann. Epidemiol. 2:675-682, 1992) reported that in man no correlations exist between blood concentrations of Δ4-androstenedione (another weak androgen) and testosterone

and fat distribution, when results were corrected per age and body mass index, thus excluding any cause-effect relationship between these two hormones and the fat distribution in man. A balancing action of androstenediol on fat mass is, therefore, quite unexpected, contrary to its protein anabolic action.

A further advantage of the present invention is that the active ingredient is substantially non toxic.

In the following, some data relating to the pharmacological trials are reported.

Pharmacological trials

Studies were carried out on 14 52-54 years old women. All women had been in amenorrhea for about 6-12 months and had low values of estradiol. Seven subjects were treated with a therapy comprising: conjugated estrogens 0.625 mg/day for 28 days plus medroxyprogesterone acetate 10 mg/day for 11 days with a one week suspension, for 8 overall cycles. The other seven subjects were administered with androst-5-ene-3β,17β-diol. Fat mass, lean body mass, bone mass, body weight were evaluated by means of DEXA HOLOGIC. In the following there are reported the mean percent values of cholesterol, HDL cholesterol, fat mass and lean body mass of the two groups of subjects before treatment and after treatments with estro-progestins and with androst-5-ene-3β,17β-diol 10 mg/day.

		Total cholesterol	HDL cholesterol	Fat mass	Lean body mass
Mean values in estro-progestin therapy	Before	214 ± 30 mg/100 ml	54 ± 12 mg/100 ml	31.4%	61.8%
	After	222 ± 20 mg/100 ml	58 ± 10 mg/100 ml	33.4%	59.6%
Mean values in andro-stenediol therapy 10 mg/day	Before	224 ± 18 mg/100 ml	56 ± 14 mg/100 ml	32.2%	60.8%
	After	211 ± 23 mg/100 ml	54 ± 12 mg/100 ml	28.8%	65%

The differences between basal values and values after treatment were significant both for fat mass ($p<0.01$) and for lean body mass ($p<0.01$) in patients treated with androst-5-ene-3β,17β-diol. Total cholesterol was found to have a tendency to decrease, whereas HDL cholesterol remained unchanged.

In patients who received treatment with estro-progestins basal values were not different from post-treatment values. No significant differences in bone mass of the subjects treated with the two different therapies were found, in that in both cases bone mass remained stable or tended to increase. On the contrary, menopausal-related symptoms, such as flushing, perspiration, irritability, depression were absent in both the studied groups; the group treated with androst-5-ene-3β,17β-diol, however, being more sthenic and having a better sense of well-being.

These data suggest that estro-progestins, administered during post-menopause, are not capable of restoring the fat mass/lean body mass ratio. On the contrary, androst-5-ene-3β,17β-diol significantly increased lean body mass and reduced as much significantly fat mass. The weight of the patients and the bone mass at the end of the treatment (after 8 months) were substantially superimposable. However, the fat mass/lean body mass ratio shifted towards lean body mass.

The therapy with androst-5-ene-3β,17β-diol protracted for 8 months induced no significant changes in total cholesterol, LDL cholesterol, triglycerids and glycemia. Furthermore, no significant increases in

circulating androgens were observed: free testosterone and androstenedione only showed a slight tendency to increase, such an increase, however, being not significant at the used doses. Moreover, an improvement in sexual behaviour and well-being was observed in all the treated women, together with a reduction of asthenia in patients in which the symptom had been present.

As far as the industrial applicability is concerned, the medicaments according to the present invention are formulated as pharmaceutical compositions. Said compositions, which are a further object of the invention, will be prepared according to conventional methods known to those skilled in the art. Said methods are, for example, described in "Remington's Pharmaceutical Sciences Handbook", Mack Publishing Company, New York, U.S.A.

The compositions according to the invention contain an effective amount of active ingredient in admixture with pharmaceutically acceptable carriers and excipients. More specifically, the compositions will be in the form of unitary dosages suitable for the administration of up to 30 mg of androst-5-ene-3β,17β-diol, preferably 10 mg, daily. The dosage units can be single or subdivided in the therapeutical daily dose.

Examples of pharmaceutical compositions include tablets, capsules, pills, solutions, syrups, injectable forms, topical forms such as creams or ointments, or transdermal formulations.

Transdermal formulations are particularly preferred, and they are a further object of the invention. Such formulations have a good compliance and,

more interestingly, are particularly suitable for long-term treatments, also considering the active principle half-life. These formulations provide an effective, homogeneous, cutaneous absorption, and they cause no blood peaks, as often occurs in topical treatments with conventional formulations.

The transdermal formulations according to the invention consist of a solution of androst-5-ene-3β,17β-diol in a mixture of an alcohol (preferably absolute ethanol) and a glycol (preferably propylene glycol), added with one or more polymeric compounds, such as cellulose derivatives (for example ethyl cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose), polyacrylic and/or polymethacrylic acid esters and the like, and further containing the conventional excipients and/or plasticizers.

Said formulations will be in contained in containers equipped with a dispenser to apply the correct dose of the formulation to the skin. After evaporation of the solvent, the film remaining on the skin releases the active principle in the space of 24 hr and can subsequently be removed by the usual detergents.

The following examples further illustrate the invention.

EXAMPLE 1

Compound	% w/w
Androst-5-ene-3β,17β-diol	1.000
Ethyl cellulose	7.000
Propylene glycol	2.000
Stearic acid	4.000
Hydroxypropyl cellulose	1.000

Colloidal silica	1.000
Absolute ethanol	q.s. to 100

The solution is distributed in an aluminium container coated internally with epoxy phenolic resins, equipped with a dispenser.

The formulation was characterized by an in vitro dissolution test (Dissolution test USP) and the release kinetics of the active principle during an 8 hr time was evaluated (see figure).

EXAMPLE 2

Compound	% w/w
Androst-5-ene-3β,17β-diol	0.500
Methacrylic acid esters	5.000
Povidone	2.000
Propylene glycol	2.000
Stearic acid	4.000
Hydroxypropyl cellulose	1.000
Colloidal silica	1.000
Absolute ethanol	q.s. to 100

The solution is distributed in an aluminium container coated internally with epoxy phenolic resins, equipped with a dispenser.

EXAMPLE 3

Compound	% w/w
Androst-5-ene-3β,17β-diol	1.000
Methacrylic acid esters	5.000
Propylene glycol	2.000
Cetyl alcohol	4.000
Hydroxymethyl cellulose	1.000
Colloidal silica	1.000

Absolute ethanol	q.s. to 100

The solution is distributed in an aluminium container coated internally with epoxy phenolic resins, equipped with a dispenser.

CLAIMS

1. The use of androst-5-ene-3β,17β-diol for the preparation of a medicament useful for the treatment of deficiencies of delta 5-androsten hormones.

2. The use of androst-5-ene-3β,17β-diol for the preparation of a medicament useful for controlling the post-menopausal syndrome.

3. The use of androst-5-ene-3β,17β-diol for the preparation of a medicament useful for controlling osteoporosis.

4. The use of androst-5-ene-3β,17β-diol for the preparation of a medicament useful for inducing a decrease in fat mass and an increase in the lean body mass in menopausal women.

5. The use as claimed in claim 2, wherein androst-5-ene-3β,17β-diol is in combination with other active principles.

6. The use as claimed in claim 5, wherein said other active principles are estrogens and/or estro-progestins.

7. The use of androst-5-ene-3β,17β-diol for the preparation of a medicament useful for inducing a decrease in fat mass and an increase in the lean body mass in an ageing humans.

8. Pharmaceutical composition containing an effective amount of androst-5-ene-3β,17β-diol as active ingredient in admixture with pharmaceutically acceptable excipients and carriers.

9. Pharmaceutical composition as claimed in claim 6, containing an amount of active ingredient from 5 to 30 mg for a daily administration.

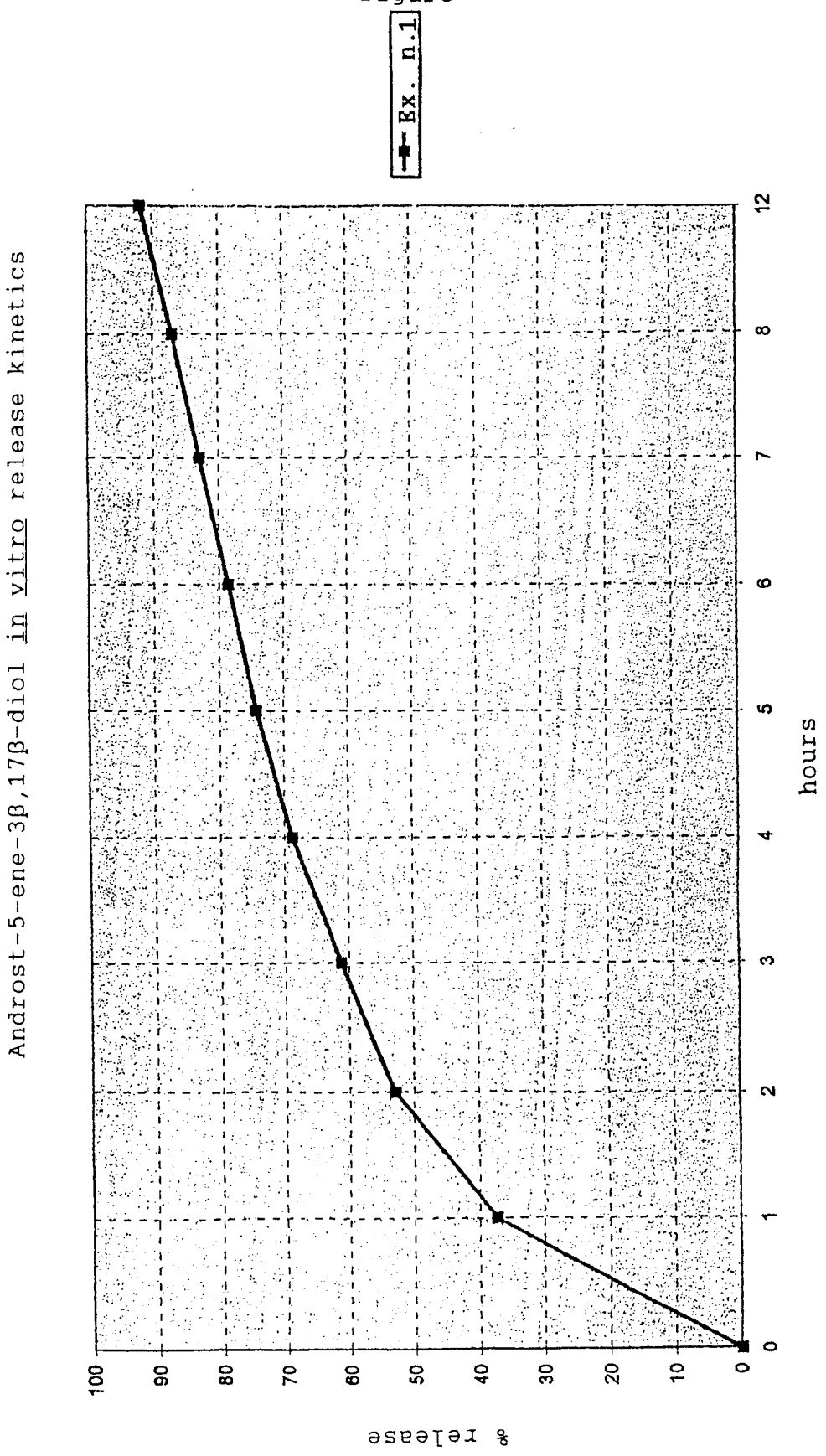
10. Pharmaceutical compositions as claimed in claim 8 or 9 for the transdermal administration.

11. Transdermal formulations as claimed in claim 10, consisting of a solution of androst-5-ene-3β,17β-diol in a mixture of an alcohol and a glycol, added with one or more polymeric compounds, selected from polyacrylic and/or polymethacrylic acid esters and the like, and further containing the conventional excipients and/or plasticizers.

12. Transdermal formulations as claimed in claim 11, wherein the alcohol is absolute ethanol, the glycol is propylene glycol and the cellulose derivatives are selected from ethyl cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose.

13. Composition as claimed in claim 8 or 9 for the oral administration.

figure


Androst-5-ene-3β,17β-diol in vitro release kinetics
Ex. n.1
% release
hours
0
10
20
30
40
50
60
70
80
90
100
0
1
2
3
4
5
6
7
8
12

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP 98/03392

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/565

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 6 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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 206 008 A (LOTIA) 27 April 1993 see column 12, line 23 - line 32 see column 12, line 48 - line 52 see claims 2,10 see column 14, line 31 - line 35 --- -/--	8-13

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

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
27 October 1998	09/11/1998

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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X	S.YOSHIMOTO ET AL.: "Clinical effects of metharmon F for postmenopausal women with climacteric symptoms: its relationship with serum level of hormones" DIALOG(R) FILE 155: MEDLINE(R), ACCESSION NUMBER 04630234: HORUMON TO RINSHO, vol. 31, no. 8, August 1983, pages 815-822, XP002082223 see abstract	1-13
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X	US 5 478 566 A (LORIA) 26 December 1995 see column 4, line 16 - line 22 see column 4, line 28 - line 32 see examples 5,6	8-13
X,P	US 5 656 286 A (MIRANDA ET AL.) 12 August 1997 see column 12, line 41	8-13

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Information on patent family members

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