

Clarke, Modet & Co.

COLOMBIA
E-MAIL: clarkemodet@clarkemodet.com.co
SANTAFÉ DE BOGOTÁ, A.A

71 2A
SUPERINDUSTRIA Y COMERCIO

Radicación : 00043097 00000001

Folios: 210

Fecha (ATD): 2000-09-08 18:42:06

Trámite : 002 PATENTES D 1 REGISTRO/ 323 COMPLETOS

Dep. deencia: 2020 DIVISION DE NUEVAS CREACIONES

SEÑORES
DIVISION DE NUEVAS CREACIONES
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
E. S. D.

COD:08

RE.: SOLICITANTE: WATSON PHARMACEUTICALS INC.
SOLICITUD N°. 00043097/
PATENTE: ADMINISTRACIÓN DE ESTEROIDES ANDROGENICOS NO
ORALES A MUJERES
PRIORIDADES: US/138,851; 60/138,854; 60/139,323 DE JUNIO 11, 1999
FECHA DE SOLICITUD: JUNIO 9 DE 2.000

ASUNTO: PRESENTACIÓN PRIORIDAD

DILIA RODRIGUEZ D'ALEMAN, en mi condición de apoderada de la sociedad solicitante, en esta oportunidad por el presente escrito me permito presentar:

- Copia certificada de la prioridad Estadoudinense reivindicada N°.60/138,851 de Junio 11 de 1.999.
- Copia certificada de la prioridad Estadoudinense reivindicada N°.60/138,854 de Junio 11 de 1.999.
- Copia certificada de la prioridad Estadoudinense reivindicada N°.60/139,323 de Junio 11 de 1.999.
- Traducción al Español de las mencionadas prioridades.

Estas prioridades están siendo presentadas dentro del término de 3 meses que exige el Convenio de Paris, toda vez que la solicitud fué radicada el 9 de Junio de 2.000.

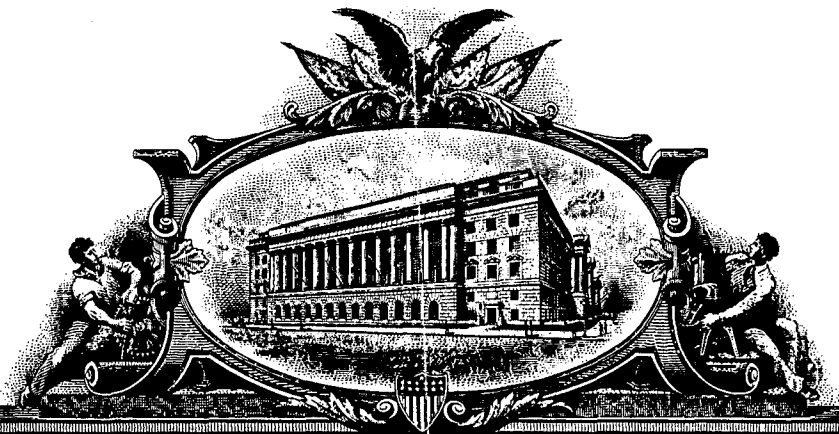
Ruego a usted continuar con el presente trámite.

Señor Jefe,



DILIA RODRIGUEZ D'ALEMAN
LCD/srr
P- 343

PA 268643



THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

June 28, 2000

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: 60/138,851

FILING DATE: June 11, 1999



**By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS**

T. LAWRENCE

Certifying Officer

PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISION APPLICATION under 37 CFR 1.53 (b)(2).

Docket Number	T7798	Type a plus sign (+) inside this box →	+
---------------	-------	--	---

INVENTOR(S)/APPLICANT(S)			
LAST NAME	FIRST NAME	MIDDLE INITIAL	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)
Mazer	Norman	A.	4641 S. Hunters Ridge Circle Salt Lake City, Utah 84124

TITLE OF THE INVENTION (280 characters max)

A METHOD OF COADMINISTERING ORAL ESTROGEN AND PARENTERAL ANDROGENIC STEROIDS TO WOMEN TO MAINTAIN FREE TESTOSTERONE WITHIN PHYSIOLOGICAL RANGE

CORRESPONDENCE ADDRESS

M. Wayne Western
THORPE, NORTH & WESTERN, L.L.P.
P.O. BOX 1219
SANDY

STATE	UTAH	ZIP CODE	84091-1219	COUNTRY	USA
-------	------	----------	------------	---------	-----

ENCLOSED APPLICATION PARTS (check all that apply)

☒ Specification (Number of Pages) 56 ☐ Small Entity Status

☒ Drawing(s) (Number of Pages) 2 ☐ Other (specify)

METHOD OF PAYMENT (check one)

☒ A check or money order is enclosed to cover the Provisional filing fees

☒ The commissioner is hereby authorized to charge filing fees and credit Deposit Account Number: 20,0100

PROVISIONAL FILING FEE AMOUNT (\$) **\$150.00**

Deficiencies Only

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

- ☒ No.
- ☐ Yes, the name of the U.S. Government agency and the Government contract number are: _____

Respectfully submitted,

SIGNATURE M. Wayne Western Date 6/11/99 Express No. **EL163093562US**

TYPED or PRINTED NAME M. Wayne Western REGISTRATION NO. 22,188
(if appropriate)

☒ Additional inventors are being named on separately numbered sheets attached hereto

PROVISIONAL APPLICATION FILING ONLY

Burden Hour Statement: This form is estimated to take 2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Office of Assistance Quality and Enhancement Division, Patent and Trademark Office, Washington, DC 20231 and to the Office of Information and Regulatory Affairs, Office of Management and Budget (Project 0651-00XX), Washington, DC 200503 DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS SENT TO: Commissioner of Patents and Trademarks, Washington, DC 20231

A/PROV 73

1c541 U.S. PTO
60/138851
06/11/99

06/11/99
3c674 U.S. PTO

06/11/99
3c674 U.S. PTO

26 7 29

5

BACKGROUND

10

There are a variety of conditions in which women express hormonal imbalance. Women who are menopausal, either naturally or as a result of ovarian failure or loss (e.g., secondary to hysterectomy, surgical oophorectomy or chemotherapy), frequently develop estrogen and testosterone deficiencies with their attendant undesirable effects. In these women, the need for estrogen replacement therapy (ERT) is determined by symptoms developed by a woman or, in some cases, by a blood test to determine serum estrogen levels.

15

Another situation in which women may express hormonal imbalance is when they are receiving estrogen-containing oral contraceptives. By suppressing ovarian function, oral contraceptives diminish testosterone production resulting in androgen deficiency in these pre-menopausal women.

20

Use of oral estrogens causes an increase in a woman's sex hormone binding globulin (SHBG). SHBG is a protein produced by the liver that tightly binds estrogen and testosterone in the blood. In its bound state, the sex hormone is not available to exert its biological action at

RPE, NORTH & WESTERN, LLP

P.O. Box 1219

Sandy, Utah 8491-1219

Telephone (801) 566-6633

77 88

5 receptors in target tissues. Not only is SHBG-bound hormone
not available to bind to receptors, it is also not available
for metabolic clearance. Hence, women receiving oral
estrogen therapy can become functionally testosterone
deficient for two reasons. First, estrogen administration
10 lowers or suppresses the pituitary luteinizing hormone (LH),
which stimulates the ovarian production of testosterone.
Second, by increasing SHBG levels, the availability of
testosterone is diminished or deficient.

In contrast to the effects of oral estrogen
15 administration, SHBG does not increase when estrogens are
provided by non-oral delivery routes, such as transdermal
delivery of estrogens. A comparison of mean SHBG levels in
oophorectomized women receiving either no estrogen
replacement therapy, transdermal estradiol (0.1 mg/day) or
20 oral conjugated equine estrogen (1.25 mg/day) is given in
Table 1.

78 9 8

5 Table 1

Hormone data (mean $\pm$ SEM) in three groups of surgically menopausal women evaluated in pharmacokinetic studies of testosterone matrix patches. Each woman received 300 mcg/day of testosterone delivered transdermally from a matrix patch.

10

Hormone unit	Transdermal E2 (0.1 mg/day)	Oral E2 (2 mg/day)	Oral CEE (2 mg/day)
Baseline SHBG Levels (nmol/L)	85.6 $\pm$ 9.6	90.8 $\pm$ 12.9	226.3 $\pm$ 13.5
Change in SHBG (nmol/L)	57.2 $\pm$ 4.4	53.6 $\pm$ 7.2	70.8 $\pm$ 9.6
Change in T (ng/mL)	4.60 $\pm$ 0.40	4.20 $\pm$ 0.70	2.56 $\pm$ 0.30

15

In the above table:

20

- E2 is estradiol
- T is testosterone
- CEE is conjugated equine estrogens

25

As shown in Table 1, SHBG levels in the oral estrogen group are approximately 2.5-fold larger than the other groups and exceed the upper limits of the normal range. In the transdermal estradiol group, SHBG levels are comparable

80 # 89

5 connote the functional level of testosterone since it is the more commonly measured serum component.

The greater increase in total testosterone levels associated with oral estrogen administration is presumably due to the decrease in testosterone clearance that results from the elevation in SHBG levels and the corresponding reduction in the free fraction of testosterone. Conversely, the smaller increase in free testosterone levels with oral estrogen administration indicates that the reduction in the free fraction exceeds the reduction in testosterone clearance.

The latter is a new and unexpected finding that could not have been predicted from earlier studies of testosterone clearance. As a general consequence of these phenomena, one would expect that for a given regimen of parenteral testosterone delivery to women, total testosterone will increase while free testosterone will decrease as a function of increasing SHBG levels. This finding is illustrated with individual patient data compiled from three studies in which women on oral or transdermal estrogen received transdermal

82 13 45

5 defined ranges such as described by Ebert, et al. in U.S.
Patent 5,460,820. This range was reported to be 50-500
mcg/day for testosterone from a transdermal patch dosage
form, with or without the concomitant administration of
estradiol from the same patch. The present invention is
10 mainly directed to free testosterone levels. Two copending
applications, filed under Thorpe, North & Western docket
numbers T7797 and T7118 on even date herewith, are directed
to total testosterone levels and delivery rates of
testosterone associated with SHBG elevation attendant with
15 orally administered estrogens.

In women who have a uterus, it is imperative that they
receive a concomitant progesterone, as unopposed estrogen
use is associated with endometrial hyperplasia which can
lead to uterine cancer. Progesterone and synthetic analogs
20 thereof may prevent this unwanted estrogen effect.
Progestins are also utilized in oral contraceptives.

The oral administration of estrogen to females,
particularly postmenopausal or oophorectomized women (i.e.
women who have had one or both of their ovaries removed), is

THORPE, NORTH & WESTERN, LLP
P.O. Box 1219
Sandy, Utah 8491-1219
Telephone (801) 566-6633

83 74
88

5 common. In the context of estrogen replacement therapy,
researchers and medical practitioners have long recognized
the need to administer estrogen to make up for or supplement
the production of estrogen in women who have need thereof.
Conjugated estrogens, in dosage ranges of about 0.02 to 3.0
10 mg/day (or the equivalent of other estrogens, such as
micronized estradiol or ethinyl estradiol, to obtain the
same response) are orally administered to supplement
decreasing or lack of ovarian function. Synthetic progestin,
such as norethindronl acetate, can be administered orally or
15 transdermally to prevent endometrial hyperplasia. To control
conception in the case of oral contraceptives, ethinyl
estradiol is administered in a regimen known in the art.

However, it is recognized that merely supplementing
estrogen is not sufficient to maintain a woman's health and
20 well being. Many women continue to experience symptoms such
as loss of sexual desire, diminished vital energy, a
diminished sense of well-being, bone loss that is not
completely ameliorated by estrogen treatment, and loss of
muscle strength and mass.

ORPE, NORTH & WESTERN, LLP

P.O. Box 1219

Sandy, Utah 8491-1219

Telephone (801) 566-6633

87-18-90

5 loss, decreases vasomotor instability, and may enhance
certain cognitive abilities. The present invention is drawn
to attaining these goals by administration of parenteral
androgenic steroids to women receiving oral estrogen.

10 SUMMARY OF THE INVENTION

One object of the present invention is to provide a
method of improving health in a woman comprising
coadministering effective amounts of estrogen and androgenic
steroids characterized in that the estrogen is administered
15 orally and the androgenic steroid is administered
parenterally. In a related aspect, an object of the
invention is to provide a method of improving health in a
woman receiving estrogen orally in accordance with a regimen
(e.g., ERT or oral contraceptive), the method comprising
20 administering to the woman an androgen steroid parenterally.
Estrogen, based on conjugated estrogen, is typically
administered orally in a dosage range of between about 0.3
to 3.0 mg/day in women receiving ERT. In an oral
contraceptive context, estrogen is typically administered in

ORPE, NORTH & WESTERN, LLP

P.O. Box 1219
Sandy, Utah 8491-1219
Telephone (801) 566-6633

88-14-91

5 the form of ethinyl estradiol in a dosage range of between
about 0.02 to 0.035 mg/day. The parenteral administration
of androgenic steroid is in a dosage range that is
sufficient to achieve and maintain the free testosterone (FT)
serum levels in the woman, based on native testosterone, in
10 a range of between about 0.5 and about 15 pg/mL. As will be
discussed below, because of the surprising effect of SHBG in
women receiving oral estrogen, the levels of delivered
testosterone and total serum testosterone required to obtain
the desired FT levels is higher than previously expected.
15 Dosage forms of other estrogens, for example
micronized ethinyl estradiol, and other androgens, for
example, methyl testosterone, are formulated to yield an
equivalent response to conjugated estrogen and testosterone.

20 Another object of the present invention is to improve
health in a woman comprising coadministering effective
amounts of oral estrogen and parenteral androgenic steroids,
wherein the improvement of health is manifest by one or more
of the following parameters: restoration or enhancement of
sexual desire, restoration or enhancement of stimulation to

89 20 92

5 sexual organs, restored or enhanced ability to achieve
orgasm, restoration or enhancement in pleasure in sexual
activity, restoration or enhancement of vital energy and
sense of well-being, improvement or enhancement in muscle
tone, skin and hair appearance, restoration or improvement
10 in cognition, increased bone mineral density, improvement in
blood lipids, improvement in cardiovascular tone and
responsivity, and reduction in vasomotor instability.

These and other objects are accomplished by providing a
method of improving health in a woman comprising
15 coadministering effective amounts of estrogen and androgenic
steroids characterized in that said estrogen is administered
orally and said androgenic steroid is administered
parenterally.

Estrogen, based on conjugated estrogen, is typically
20 administered orally in a dosage range of between about 0.02
to 3.0 mg/day, the specific dosage being dependent on the
nature of the estrogen background (e.g., ERT or oral
contraceptive), as well as individual patient needs. The
androgenic steroid is administered in a dosage range

COPIES DESTROYED

92-23
A5

5 DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to methods for
coadministering oral estrogen and parenteral androgenic
steroids, in effective amounts, to women who are in need of
supplementation, such as women exhibiting symptoms
10 attributable to the deficiency or imbalance of estrogen and
androgenic hormones due to menopause and/or natural aging or
as a result of hysterectomy, oophorectomy or ovarian failure
(e.g., consequent to chemotherapy), or adrenal
insufficiency.

10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100
105
110
115
120
125
130
135
140
145
150
155
160
165
170
175
180
185
190
195
200
205
210
215
220
225
230
235
240
245
250
255
260
265
270
275
280
285
290
295
300
305
310
315
320
325
330
335
340
345
350
355
360
365
370
375
380
385
390
395
400
405
410
415
420
425
430
435
440
445
450
455
460
465
470
475
480
485
490
495
500

15 The invention relates to a method of coadministration
of oral estrogen and parenteral androgenic steroids to women
in need to alleviate symptoms attributable to the deficiency
or imbalance of estrogen and androgenic hormones and to
provide optimal effects on health, sexual function and well-
being. With respect to androgenic hormones, the method will
20 comprise administering androgen at levels sufficient to
provide free testosterone levels of from about 0.5 to about
15 pg/ml. Preferably the free testosterone levels will be
from about 1 to about 12 pg/ml, more preferably from about 3

93 24 90

5 to about 12 pg/ml, most preferably from about 5 to about 10
pg/ml. Of course, the actual serum FT level in a given
patient will be that sufficient to alleviate the symptoms
associated with androgen deficiency. As indicated, the
amount of testosterone delivered, as well as the total serum
10 testosterone levels, required to achieve these levels may be
higher than previously expected, due to the elevated SHBG
levels in women receiving oral estrogen.

5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100

Before the present methods of improving health in a
woman are disclosed and described, it is to be understood
15 that this invention is not limited to the particular process
steps and materials disclosed herein, as such process steps
and materials may vary somewhat. It is also to be
understood that the terminology employed herein is used for
the purpose of describing particular embodiments only and is
20 not intended to be limiting since the scope of the present
invention will be limited only by the appended claims and
equivalents thereof.

014 25 97

5 In describing and claiming the present invention, the following terminology will be used in accordance with the definition set out below.

As used within the context of this invention, the term "coadministration" means administration of multiple active substances to one individual, either simultaneously or sequentially. Thus, the term includes any situation in which women are receiving oral estrogen and parenteral androgen. The term does not imply that the estrogen and androgen actives have to be administered at the same time.

10 Rather, as long as a woman is receiving estrogen orally, administration of parenteral androgen to maintain the desired free testosterone levels will be within the present definition for "coadministration". For example, parenteral administration of androgenic steroids to an individual who has previously been placed on oral estrogen therapy is within the meaning of "coadministration" in the present application. Thus, it is clear that the estrogen and the androgen actives need not be provided in a single product to be "coadministered".

RECEIVED FEB 10 1980

ORPE, NORTH & WESTERN, LLP

P.O. Box 1219
Sandy, Utah 8491-1219
Telephone (801) 566-6633

9/5 26
98

5 As used within the context of this invention, the terms
"androgenic steroid", "testosterone agent" or "testosterone"
(when used generically), must be taken in context and are
generally meant to encompass any androgenic steroid that is
functional in reducing signs and symptoms of testosterone
10 deficiency in females. Members selected from the group
consisting of native testosterone, testosterone esters,
methyltestosterone and other 17-alkylated versions, methyl
testosterone esters, androstenedione, adrenosterone,
dehydroepiandrosterone, fluoxymesterone, methandrostenolone,
15 17 α -methylnortestosterone, norethandrolone,
dihydrotestosterone, oxymetholone, nandrolone and its
derivatives, stanozolol, ethylestrenol, oxandrolone,
bolasterone and mesterolone are representative of androgenic
steroids. Of this group testosterone, dihydrotestosterone,
20 testosterone esters and methyltestosterone are preferred.
Representative esters include the propionate, phenylacetate,
enanthate and cypionate esters of testosterone.

The term "parenteral" refers to any route of
administration other than the gastrointestinal tract and

ORPE, NORTH & WESTERN, LLP

P. O. Box 1219

Sandy, Utah 8491-1219

Telephone (801) 566-6633

99 30 402

5 free or bioavailable testosterone, i.e. the concentration of
non-SHBG bound testosterone, can be indicative of the
functional level of testosterone in the blood. Total serum
testosterone can be measured by RIA at a clinical
laboratory, using standard techniques, for example, the RIA
10 procedure used by Endocrine Sciences, Inc. (Calabasas Hill,
CA). According to such procedure, serum samples are
extracted with hexane:ethyl acetate. The extract is then
applied to Al_2O_3 micro columns. The columns are washed with
hexane containing 0.55% ethanol. Finally, testosterone is
15 specifically eluted using hexane containing 1.4% ethanol.
Duplicate aliquots are then taken for RIA. Purified samples
are incubated with an antibody made to a testosterone-3-
oxime-BSA conjugate. Free and antibody-bound testosterone
in each sample is calculated from a curve generated by
20 purified testosterone standards. Sensitivity of the method
is 3 ng/dL when a normal 0.5 ml serum aliquot is used.

The term "serum bioavailable testosterone" refers to
the fraction of testosterone in the serum that is not bound
by SHBG, and can be measured by standard commercial

laboratories, for example, the following procedure at Endocrine Sciences, Inc. Sample preparation begins with an ammonium sulfate precipitation of the SHBG-bound testosterone in the serum sample. Then, the amount of testosterone remaining in the sample is determined by using the total testosterone remaining in the sample, using the total testosterone determination procedure.

The term "serum free testosterone" refers to the fraction of testosterone in the serum that is not protein bound and is measured according to the following procedure at, for example, Endocrine Sciences, Inc. Serum is placed inside a semipermeable dialysis bag and dialyzed against a buffer containing tritium labeled testosterone outside the dialysis bag. The percent free testosterone is calculated from the ratio of radioactivity outside the bag versus inside the bag. This percent free testosterone, multiplied by the total testosterone in the serum and corrected for units, results in the concentration of free testosterone in the serum. Protein levels are checked in the dialysate to

101 22 404

5 be sure the dialysis bag has not leaked. The minimum reportable free fraction is 0.1 percent free.

As used herein, "SHBG" is the protein sex hormone binding globulin in the serum that can be measured by a commercial laboratory standard method, e.g., the immunoradiometric assay from Endocrine Sciences, Inc. A monoclonal antibody made to human SHBG is coated onto plastic beads. The sample and a different SHBG monoclonal antibody, which is labeled with ^{125}I , are incubated overnight with the antibody coated bead. SHBG in the sample and the standard form BEAD-ANTIBODY-SHBG-ANTIBODY ^{125}I sandwiched complexes, attaching ^{125}I lable to the beads. The beads are then washed to removed unbound label, and counted.

As used herein, "transdermal" or "percutaneous" delivery means delivery of an androgenic steroid by passage into and through the skin tissue. Terms "skin," "derma," "epidermis," and the like shall be used interchangeably unless specifically stated otherwise.

The term "diffusional communication" intends that when a transdermal androgenic steroid device of the invention is

102-35
105

5 placed on the skin of a woman, there is a direct or indirect
diffusional pathway by which the androgenic steroid can
migrate from the hormone-containing elements of the device
to the skin of the wearer.

10 By "delivery system," "patches" or any similar
terminology is meant a matrix or container type of delivery
device which are used to transdermally deliver defined doses
of androgenic steroids, over a specific application period.
A preferred patch for administering androgen steroid in
accordance with this invention is a matrix-type patch which
15 comprises an occlusive backing that is impermeable to the
androgen steroids and defines the face or top surface of the
patch and a solid or semisolid matrix layer comprised of a
homogeneous blend of the hormone, a polymeric pressure
sensitive adhesive carrier, and optionally one or more skin
20 permeation enhancers. Matrix patches are known in the art
of transdermal drug delivery. Examples without limitation,
of transdermal patches are those described or referred to in
U.S patent Nos. 5,122,383 and 5,460,820 and are hereby
incorporated by reference.

103 24 406

5 Several parenteral modes of delivery may be employed
for the androgenic compound. These include: transdermal
delivery via patch, gel, cream, ointment, film, or other
means of application to the skin; transmucosal routes,
including sublingual or buccal delivery, which afford more
10 long-lasting blood levels than oral delivery; intramuscular
injection; and subdermal implants. The preferred means for
parenteral administrations are by the transdermal route,
intramuscular injection, or subdermal implant. The most
preferred means for transdermally administering the
15 androgenic steroids are the matrix or container type of
patches. Of these systems, the matrix type patches are most
preferred.

For transdermal administration, skin permeation
enhancer(s) may be included in the formulations to enhance
20 the level of skin flux of the hormone. Examples, without
limitation, of skin permeation enhancers that may be used
in, e.g., matrix patches, are those described or referred to
in U.S. Patent Nos 5,122,383 and 5,153,997, the disclosures
of which as they relate to skin permeation enhancers are

104 35 107

5 incorporated by reference. The enhancer will usually
constitute 1 to 20 wt % of the adhesive carrier forming the
matrix.

Patches for transdermal delivery of androgen steroids
may be manufactured by conventional techniques used in the
10 art of transdermal drug delivery devices. For instance, the
hormones, carrier, and enhancers may be mixed in the desired
proportions to form a homogeneous mixture and then cast or
otherwise applied to a backing layer by lamination to a
release liner layer.

15 Obviously, the need for supplementing estrogen and
androgenic steroids should be determined by a physician or
other health care professional based on monitoring signs and
symptoms of estrogen and testosterone deficiency. Not every
female will exhibit the same symptoms and it is possible
20 that testosterone levels might even be within physiological
ranges but, based on other factors, for example, increased
SHBG, testosterone deficiency may still be diagnosed. Such
symptoms might include, but not be limited to, global loss
of sexual desire, decreased sensitivity to sexual

105 30 108

5 stimulation in the nipples and in the clitoris, decreased
arousability and capacity for orgasm, diminished vital
energy and sense of well-being, and, loss of muscle tone.
Some women also notice other symptoms such as thinning and
loss of pubic hair, genital atrophy not responsive to
10 estrogen, dry and brittle scalp hair, and dry skin. Other
symptoms, while less documented, include increased risk for
cardiovascular and coronary heart disease, decreased
cognitive abilities and dry eyes in patients suffering from
Sjogren's syndrome. Women who are receiving oral estrogens
15 can also benefit from androgen therapy since it may reduce
the breast tenderness that can occur with estrogen usage.
Owing to the known breast tissue antiproliferative effects,
androgens may also reduce the excess risk of breast cancer
associated with estrogen use.

20 It is therefore highly desirable, if not imperative,
that testosterone supplementation for a female patient be
based on a diagnosis by a physician who prescribes the mode
of application, dosage and duration of treatment.

106 57 109

5 As described above, one aspect of the present invention
is to provide a method of improving health in a woman
comprising coadministering effective amounts of estrogen and
androgenic steroids characterized in that the estrogen is
administered orally and the androgenic steroid is
10 administered transdermally. Estrogen, based on conjugated
estrogen, is administered orally in a dosage range of
between about 0.02 to 3.0 mg/day. For some women,
particularly those women who are not in need of control of
vasomotor symptoms, the frequency of dosing may be less
15 often than once per day, which may still maintain benefits
for bone health. In the case of oral contraceptive use,
ethinyl estradiol is typically given cyclically in a 21 day
on, 7 day placebo regimen.

20 The oral administration of estrogens increases the
levels of SHBG, which in turn decreases the bioavailable or
free testosterone level. Since additionally, SHBG-bound
androgen is not as readily available to metabolizing
enzymes, metabolic clearance rates are decreased. However,
the net effect, which was discovered experimentally, is that

107 38 1-10

5 the oral estrogens effectively decrease the levels of
circulating functional testosterone(i.e. free or
bioavailable testosterone levels) in a woman's body via an
increase in the SHBG, since the steady state levels of free
or bioavailable testosterone are affected more strongly by
10 the binding to SHBG rather than reduced metabolic clearance
rates. This has not been previously appreciated and is the
basis for achieving supra-physiological levels of total
testosterone in some women receiving estrogen therapy.

15 The administration of androgenic steroid is in a dosage
range equivalent to the dose response obtained from
administering testosterone in a dosage range resulting a
serum level of about 0.5-15 pg/mL of free testosterone(FT),
the exact value varying from patient to patient, and
depending on the methodology used. The range 0.5-15 pg/mL
20 free testosterone(FT) corresponds to laboratory values
obtained using a standard analytical routine clinic
measuring techniques.

Synthetic androgens serum level may be measured using
gas chromatography combined with mass spectrometry. Those

108 34 11

5 skilled in the art will be able to utilize such analytical
methods to determine the serum levels of these synthetic
androgens.

10 Serum free testosterone (FT), as determined by analysis
of blood or other body fluid, will generally refer to native
testosterone. Based on the above dosages and laboratory
tests, one skilled in the art can readily determine what
amount of a particular androgenic steroid or testosterone
derivative to administer to achieve the desired serum FT
levels. What is important is that the dose of the
15 androgenic steroid or testosterone derivative must be
sufficient to overcome, or at least alleviate, the
deficiency being monitored or treated, without administering
too great a dosage. However, it is an object of this
invention to provide a method of treating testosterone
20 deficiencies in women who are taking oral dosages of
estrogen to alleviate physiological symptoms attributable to
the deficiency or imbalance of estrogen and androgenic
hormones and to provide optimal effects on health, sexual
function, and well-being. Further, since the oral estrogen

109
112

5 increases the amount of SHBG, this invention relates to a
method for overcoming this effect. Due to the natural
variation in hormone sensitivity, the exact dosage is not as
critical as is the obtaining of the resultant physiological
response for that particular patient, which can correspond
10 to a free testosterone serum level of about 0.5-15 pg/mL
free testosterone. What is more important, due to the high
SHBG environment, is that this level corresponds to an
effective level of biologically active testosterone
component. As indicated, the required dosage may be higher
15 than that previously taught by the art.

Too high a dosage of testosterone or other androgen
steroids, or application of a dosage for too long a period
of time may be manifest by symptoms of testosterone excess,
i.e. irritability, clitoral enlargement, increased facial
20 hair and lowering of the voice. The incidence of side
effects depends somewhat on the woman's own sensitivity to
androgens, but is also dependent on the level of
bioavailable or free testosterone at the target tissue.
Owing to the potential for side effects, the lowest

110 113

5 concentration that can bring about the desired effects is preferred. Generally speaking, the guidelines contained in the present invention should yield a satisfactory safety profile.

10 While the invention encompasses the utilization of testosterone, testosterone esters and methyltestosterone, it may be beneficial to utilize methyltestosterone or similarly non-aromatizable androgens, such as dihydrotestosterone, when it is preferred that estradiol levels be maintained at a low level. Methyltestosterone does not tend to aromatize
15 in situ into estradiol, whereas small amounts of testosterone may be converted to estradiol. Use of methyltestosterone is of particular value, for example, in women who develop testosterone deficiency as a result of ovarian failure following chemotherapy for breast cancer and
20 who need to keep their estrogen levels as low as possible. However, while the following examples primarily illustrate the use of testosterone, testosterone esters and methyltestosterone, such are not intended to be a limitation on the invention, as other androgenic steroids may also be

ORPE, NORTH & WESTERN, LLP

P. O. Box 1219

Sandy, Utah 8491-1219

Telephone (801) 566-6633

111 112 114

5 utilized to bring about the desired results but may need to
be monitored more carefully.

In the embodiments exemplified in the following
examples, a dosage sufficient to provide a serum level of
about 0.5-15 pg/mL of free testosterone is administered to a
10 woman receiving oral estrogen in an ERT regimen or as an
oral contraceptive. In other words, the androgenic steroid
is administered in a dosage range equivalent to the dosage
response obtained from administering sufficient native
testosterone or a testosterone ester to produce a serum
15 level of about 0.5-15 pg/mL of free testosterone and obtain
the desired response in the woman to whom it is
administered. The concentration most appropriate for a
particular woman can be determined empirically (e.g., by
varying the delivery dosage and assessing the resulting
20 effects on sexual function and general sense of well being),
usually within a serum level of about 0.5-15 pg/mL of free
testosterone.

In carrying out the present invention, upon determining
the presence of one or more signs and symptoms of

ORPE, NORTH & WESTERN, LLP

P.O. Box 1219

Sandy, Utah 8491-1219

Telephone (801) 566-6633

112 T3
445

5 testosterone deficiency in a female receiving oral estrogen
therapy (or to be placed on oral estrogen therapy), a
parenteral dose of transdermal patch containing an
androgenic steroid, such as testosterone or other androgen
as previously described, is applied in sufficient quantity
10 and for sufficient time to reduce symptoms of testosterone
deficiency or imbalance of estrogen/androgenic steroid. The
goal is to reduce symptoms of testosterone deficiency or
imbalance of estrogen/androgenic steroid.

15 In addition to transdermal testosterone patches, other
parenteral systems for delivering androgens include: intra-
muscular injections of testosterone esters, subcutaneous
implants of fused testosterone, and topical preparations of
testosterone, methyltestosterone and other androgens.
Devices and methods for those parenteral applications are
20 well known in the art.

As used herein, "application situs" means a site
suitable for topical application by means of an adhesive-
secured, sustained release device, patch, or dressing, e.g.
on the arm, back, chest, abdomen, leg, buttock, etc.

113 94 110

5 Typically the device will be designed to be worn for 1 to 14
days, more usually from 1 to 7 days. The diffusion
coefficient of the androgenic steroid in the carrier vehicle
of the device and the solubilities of the androgenic
steroids in the carrier are important factors. The
10 transdermal dose of any androgenic steroid may require minor
adjustments. However, it is to be noted that the overall
ranges for testosterone are those sufficient to achieve and
maintain overall ranges of androgenic steroid equivalent of
0.5-15 pg/mL free testosterone level. This range may vary
15 for any given androgenic steroid according to its relative
potency and bioavailability. Therefore the key to the exact
amount is that of functionality. Any androgenic dosage that
produces a serum level equivalent 0.5-15 pg/mL of free
testosterone should be effective. More than one androgenic
20 steroid or form of testosterone may be combined to achieve
the desired result. Testosterone, testosterone esters,
dihydrotestosterone and methyltestosterone, as noted above,
are the preferred androgenic steroid agents for use herein.

ORPE, NORTH & WESTERN, LLP
P.O. Box 1219
Sandy, Utah 8491-1219
Telephone (801) 566-6633

114
43
117

5 In one embodiment, the androgenic steroid is delivered
transdermally via a matrix type patch. The androgen patch
is applied to a subject who is also orally administered
estrogen in an effective quantity. The androgen is
administered in a sufficient quantity to alleviate signs and
10 symptoms attributable to the deficiency or imbalance of
androgenic hormones.

In general, estrogens will be administered orally at a
dosage that is equivalent to about 0.02 to 3.0 mg per day of
conjugated estrogen. The dose will be adjusted according to
15 an individual woman's needs and the potency of estrogen
administered. The dose of oral estrogens can be taken in a
single daily dose or in two or more smaller quantities.
Generally, for women who are experiencing vasomotor
symptoms, the lowest effective dose of estrogen is used to
20 control for vasomotor instability. Lower doses may be used
in women who do not suffer vasomotor symptoms but will
benefit from other health benefits, such as cardiovascular
and bone benefits.

115
46
148

5 Optionally, progestin is also administered to women in
need to protect against endometrial hyperplasia. The
administration of progestin can be done by any method known
in the art according to individual need. Progestins are
also essential active ingredients of many oral contraceptive
10 formulations.

15 The following examples are illustrative of the results
obtained using coadministration of oral estrogen and
parenteral androgenic steroids to alleviate physiological
symptoms attributable to the deficiency or imbalance of
estrogen and androgenic hormones in females, according to
the invention. It is to be understood that while the
invention has been described in conjunction with the
preferred specific embodiments thereof, that which follows
is intended to illustrate and not limit the scope of the
20 invention. Other aspects of the invention will be apparent
to those skilled in the art to which the invention pertains.

EXAMPLE 1

ORPE, NORTH & WESTERN, LLP
P.O. Box 1219
Sandy, Utah 8491-1219
Telephone (801) 566-6633

116
47
749

5 In surgically menopausal women between the ages of 20
and 55 years, oral estrogen and transdermal testosterone are
administered as follows. The estrogen consists of conjugated
equine estrogen (Premarin® tablets) at a daily dose of 0.625
to 2.5 mg. The transdermal testosterone is administered by
10 a matrix type transdermal patch that is applied to the
abdomen twice weekly and had a nominal delivery rate of 300
mcg/day. The duration of coadministration is 12 weeks.
After 12 weeks, this regimen improved sexual function, mood
and well-being in comparison to administration of conjugated
15 equine estrogen alone.

Serum hormone levels measured on this regimen are in
the following ranges: total testosterone (15.5 to 254.3
ng/dL), free testosterone (1.7 to 33.7 pg/mL), estradiol (5
to 280 pg/mL), and estrone (8 to 410 pg/mL). The levels of
20 sex hormone binding globulin rang from 62.7 to 563 nmol/L.
It is noteworthy that 73 percent of the women on this
regimen of oral estrogen and transdermal testosterone
achieved total testosterone levels in excess of 80 ng/dL.

117-
428
420

5 In contrast, 97 percent have free testosterone levels below
15 pg/mL.

EXAMPLE 2

10 A combination of an androgenic compound and an
estrogenic compound is administered to women who are
naturally menopausal according the following regimen:

15 Androgen: topical administration of testosterone in an
appropriate vehicle, such as a cream or ointment, that may
contain a permeation enhancer such that serum concentrations
of free testosterone are in the range of 0.5-15 pg/mL. The
androgen cream may contain cetyl esters, cetyl alcohol,
white wax, glyceryl monostearate, propylene glycol
monostearate, methyl stearate, benzyl alcohol, sodium lauryl
sulfate, glycerin, and mineral oil. The cream may optionally
20 contain a permeation enhancer such that serum concentrations
of total testosterone attained are in the range of 30 - 250
ng/dL. Each gram of the cream contains about 400 mcg
testosterone. About 1 gram of the cream is applied to the
skin or abdomina at bed time.

DRPE, NORTH & WESTERN, LLP

P. O. Box 1219

Sandy, Utah 8491-1219

Telephone (801) 566-6633

118 49 121

5 In order to control the amount of testosterone
administered, a meter dosing device can be employed. Dose
adjustments can be made on the basis of either symptom
relief, e.g. restored libido, or to achieve the desired
serum free testosterone serum concentrations. Ranges for
10 symptomatic relief may vary between 1-20 pg/mL.

Estrogenic compound: oral conjugated estrogens tablets
are given at a starting dose of 0.625 mg/day. When
necessary, doses are adjusted upward to 1.25 mg/day for
better control of symptoms, or downward to 0.3 mg/day as
15 vasomotor symptoms subside to maintain bone and serum lipid
benefits.

In women who have an intact uterus, it is important
that a background of a progesterone be present to avoid
endometrial hyperplasia that can result from unopposed
20 estrogen replacement therapy.

Benefits of combined regime of hormones may be
perceptible to the patient within the first 6 weeks of
administration, but variable responses can be expected.

ORPE, NORTH & WESTERN, LLP

P.O. Box 1219
Sandy, Utah 8491-1219
Telephone (801) 566-6633

119 80 122

5 Typically, hormones are administered on a chronic basis to maintain health.

EXAMPLE 3

10 A combination of an androgenic compound and an estrogenic compound is administered to women who are post-menopausal to alleviate signs and symptoms associated with frailty, such as the loss of bone and muscle mass and function, reduced cognitive abilities and diminished energy.

15 Androgen: intramuscular injection of 150 mg testosterone enanthate every month. Testosterone enanthate is formulated to contain 200 mg per mL in sesame oil. In order to provide 150 mg of testosterone enanthate, the injected dose is 0.75 mL.

20 Estrogen: oral estrogens are given in a range of 0.3 to 3.0 mg/day.

Administration is performed as long as benefits of treatment are desired and deemed appropriate by the prescribing physician.

120 ST
123

5

EXAMPLE 4

A combination of an androgenic compound and an estrogenic compound is administered to women with premature ovarian failure, e.g., women whose ovarian function permanently ceases prior to age 40.

10

Androgen: methyltestosterone is delivered by the buccal route at a dose of 1 mg/day to achieve an improvement in sexual function that is equi-efficacious to that produced by native testosterone at serum levels of about 50 to 300 ng/dL. The buccal tablet is a bilayer tablet consisting of a drug layer and a bio-adhesive layer (both 50 mg each). The composition of the drug layer (in weight percent) is 2% methyltestosterone, 0.75 % magnesium stearate, 0.1% FD&C yellow #6, 24% Klucel HXF, and 73.15% mannitol. The composition of the bio-adhesive layer (in weight percent) is 69.25% polyethylene oxide, 30% carbomer 934P, and 0.75% magnesium stearate. The adhesive side of the tablet is affixed to the gingiva of the upper jaw and the drug side of the tablet faces the overlying buccal mucosa. Drug is

15

20

ORPE, NORTH & WESTERN, LLP

J. Box 1219

Sandy, Utah 8491-1219

Telephone (801) 566-6633

171
82
124

5 absorbed transmucosally as the tablet dissolves over two
hours. The tablet is applied once daily after breakfast.

Estrogen: Estrace®, an oral micronized estradiol
product in tablet form, is administered by oral tablet at a
dosage of 2 mg/day to alleviate menopausal symptoms and
10 prevent bone loss.

In addition a progestin, medroxyprogesterone acetate,
is orally administered at a dose of 5 mg/day for the last
ten days of each month to induce endometrial sloughing.

The treatment is administered until the patient reaches
15 about age 55, at which time it may be modified to other HRT
regimens.

These examples are intended to be indicative only of
regimens that can be utilized. Each regimen will preferably
20 be customized to meet the needs of the patient. While the
examples have been directed primarily to the delivery of an
androgenic steroid to provide needed supplementation based
on determination of a need for such, the administration will

172 53
125

5 be concurrent with the oral administration of estrogen
formulations.

Those skilled in the art will recognize, or be able to
ascertain using no more than routine experimentation, many
equivalents to the specific embodiments of the invention
10 described herein. Such equivalents are intended to be
encompassed by the following claims.

11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100

123
54
126

5

CLAIMS

1. A method of improving health in a woman comprising
coadministering effective amounts of estrogen and androgenic
steroids characterized in that said estrogen is administered
orally and said androgenic steroid is administered by a
parenteral means.

10

2. A method according to Claim 1 wherein said
androgenic steroid is administered in a dosage sufficient to
maintain a free androgenic steroid serum level equivalent to
a free testosterone serum level of from about 0.5 to about
15 pg/mL.

15

3. A method according to Claim 2 wherein said
androgenic steroid is administered in a dosage sufficient to
maintain a free androgenic steroid serum level equivalent to
a free testosterone serum level of from about 1 to about 12
pg/mL.

20

ORPE, NORTH & WESTERN, LLP

c. O. Box 1219

Sandy, Utah 8491-1219

Telephone (801) 566-6633

124 55
127

5 4. A method according to Claim 2 or 3 wherein said
androgenic steroid is a member selected from the group
consisting of native testosterone, testosterone esters,
methyltestosterone, androstenedione, adrenosterone,
dehydroepiandrosterone, fluoxymesterone, methandrostenolone,
10 17 α -methylnortestosterone, nandrolone and its derivatives,
norethandrolone, dihydrotestosterone, oxymetholone,
stanozolol, ethylestrenol, oxandrolone, bolasterone and
mesterolone.

15 5. A method according to Claim 4 wherein said
androgenic steroid is a member selected from the group
consisting of testosterone, testosterone esters,
dihydrotestosterone and methyltestosterone.

20 6. A method according to Claim 5 wherein the
androgenic steroid is a member selected from the group
consisting of testosterone, dihydrotestosterone and
testosterone esters.

ORPE, NORTH & WESTERN, LLP

P. O. Box 1219

Sandy, Utah 8491-1219

Telephone (801) 566-6633

125 86 128

5 7. A method according to Claim 6 wherein said
androgenic steroid is testosterone.

8. A method according to Claim 5 wherein the
androgenic steroid is methyltestosterone.

10 9. A method according to Claim 5 wherein the
androgenic steroid is dihydrotestosterone.

15 10. A method according to Claim 2 or 3 wherein said
estrogen administered orally is in a dosage range of
equivalent to the dose response obtained from administering
conjugated estrogen in a dosage range of between 0.02 to 3.0
mg/day.

20 11. A method according to Claim 10 wherein said
estrogen administered orally is selected from a group
consisting of 17β -estradiol, α -estradiol, conjugated
estrogen, esterified estrogens, micronized estradiol, sodium

ORPE, NORTH & WESTERN, LLP

P.O. Box 1219
Sandy, Utah 8491-1219
Telephone (801) 566-6633

136 5X 129

5 estrogen sulfate, ethinyl estradiol, estrone, other
estrogenic steroids and derivatives and esters thereof.

10

12. A method according to Claim 11 wherein said
estrogen administered orally is a conjugated estrogen.

13. A method according to Claim 11 wherein said
estrogen administered orally is an esterified estrogen.

15

14. A method according to Claim 11 wherein said
estrogen administered orally is a micronized estradiol.

15. A method according to Claim 2 or 3 wherein said
estrogen hormone administered orally is in the form of an
oral contraceptive.

20

16. A method according to Claim 2 or 3 wherein said
improvement of physiological health is manifest by one or
more of the following parameters: restoration or enhancement
of sexual desire, restoration or enhancement of stimulation

127
58
130

5 to sexual organs, restored or enhanced ability to achieve
orgasm, restoration or enhancement of pleasure in sexual
activity, restoration or enhancement of vital energy and
sense of well-being, enhancement in muscle tone, bone
mineral density, skin and hair, and reduction in vasomotor
10 instability.

17. A method according to Claim 2 or 3 wherein
progesterone is administered concomitant with estrogen
administration.

15 18. A method according to Claim 2 or 3 wherein the
parenteral means is selected from the group consisting of
transdermal delivery means, means of topical administration
to the skin, sublingual delivery means, transbuccal delivery
20 means, transmucosal delivery means, intramuscular injection
and subdermal implants.

19. A method according to Claim 18 wherein the
parenteral means is selected from the group consisting of

128
59
131

5 transdermal delivery means, intramuscular injection, and subdermal implants.

20. A method according to Claim 19 wherein the parenteral means is intramuscular injection.

10

21. A method according to Claim 19 wherein the parenteral means is subdermal implants.

15

22. A method according to Claim 18 wherein the parenteral means is a topical cream or gel.

23. A method according to Claim 18 wherein the parenteral means is a transdermal device.

20

24. A method according to Claim 23 wherein the transdermal device is a matrix type transdermal device.

25. A method of improving health in a woman receiving oral estrogen in an oral estrogen regimen, comprising

129 60 132

5 administration of an androgenic steroid by a parenteral means to achieve a serum level equivalent to a free testosterone serum level of from about 0.5 to about 15 pg/mL.

10 26. A method according to Claim 25 wherein the serum level of the androgenic steroid is equivalent to a free testosterone serum level of from about 3 to about 12 pg/mL.

15 27. A method according to Claim 26 wherein the serum level of the androgenic steroid is equivalent to a free testosterone serum level of from about 5 to about 10 pg/mL.

130 6/139

5

ABSTRACT OF THE DISCLOSURE

The invention provides method for coadministration of oral estrogen and parenteral androgenic steroids to alleviate symptoms attributable to the deficiency or imbalance of estrogen and androgenic hormones in females. Optionally, progestins are also administered. Deficiencies are indicated by women having diminished androgen production. The method of improving health in a woman comprises coadministering effective amounts of estrogen and androgenic steroids characterized in that the estrogen is administered orally and the androgenic steroid is administered parenterally. Estrogen administered orally is in a dosage range equivalent to the dose response obtained from administering conjugated estrogens in a dosage range of between 0.02 to 3.0 mg/day. The parenteral administration of androgenic steroid is in a dosage range equivalent to the dosage response obtained from administering testosterone in a dose sufficient to cause a blood level of free testosterone, in the women, to be about .05 to about 15 pg/ml.

10

15

20

ORPE, NORTH & WESTERN, LLP

P. O. Box 1219

Sandy, Utah 8491-1219

Telephone (801) 566-6633

1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	2045	2046	2047	2048	2049	2050	2051	2052	2053	2054	2055	2056	2057	2058	2059	2060	2061	2062	2063	2064	2065	2066	2067	2068	2069	2070	2071	2072	2073	2074	2075	2076	2077	2078	2079	2080	2081	2082	2083	2084	2085	2086	2087	2088	2089	2090	2091	2092	2093	2094	2095	2096	2097	2098	2099	2100	2101	2102	2103	2104	2105	2106	2107	2108	2109	2110	2111	2112	2113	2114	2115	2116	2117	2118	2119	2120	2121	2122	2123	2124	2125	2126	2127	2128	2129	2130	2131	2132	2133	2134	2135	2136	2137	2138	2139	2140	2141	2142	2143	2144	2145	2146	2147	2148	2149	2150	2151	2152	2153	2154	2155	2156	2157	2158	2159	2160	2161	2162	2163	2164	2165	2166	2167	2168	2169	2170	2171	2172	2173	2174	2175	2176	2177	2178	2179	2180	2181	2182	2183	2184	2185	2186	2187	2188	2189	2190	2191	2192	2193	2194	2195	2196	2197	2198	2199	2200	2201	2202	2203	2204	2205	2206	2207	2208	2209	2210	2211	2212	2213	2214	2215	2216	2217	2218	2219	2220	2221	2222	2223	2224	2225	2226	2227	2228	2229	2230	2231	2232	2233	2234	2235	2236	2237	2238	2239	2240	2241	2242	2243	2244	2245	2246	2247	2248	2249	2250	2251	2252	2253	2254	2255	2256	2257	2258	2259	2260	2261	2262	2263	2264	2265	2266	2267	2268	2269	2270	2271	2272	2273	2274	2275	2276	2277	2278	2279	2280	2281	2282	2283	2284	2285	2286	2287	2288	2289	2290	2291	2292	2293	2294	2295	2296	2297	2298	2299	2300	2301	2302	2303	2304	2305	2306	2307	2308	2309	2310	2311	2312	2313	2314	2315	2316	2317	2318	2319	2320	2321	2322	2323	2324	2325	2326	2327	2328	2329	2330	2331	2332	2333	2334	2335	2336	2337	2338	2339	2340	2341	2342	2343	2344	2345	2346	2347	2348	2349	2350	2351	2352	2353	2354	2355	2356	2357	2358	2359	2360	2361	2362	2363	2364	2365	2366	2367	2368	2369	2370	2371	2372	2373	2374	2375	2376	2377	2378	2379	2380	2381	2382	2383	2384	2385	2386	2387	2388	2389	2390	2391	2392	2393	2394	2395	2396	2397	2398</
------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	--------

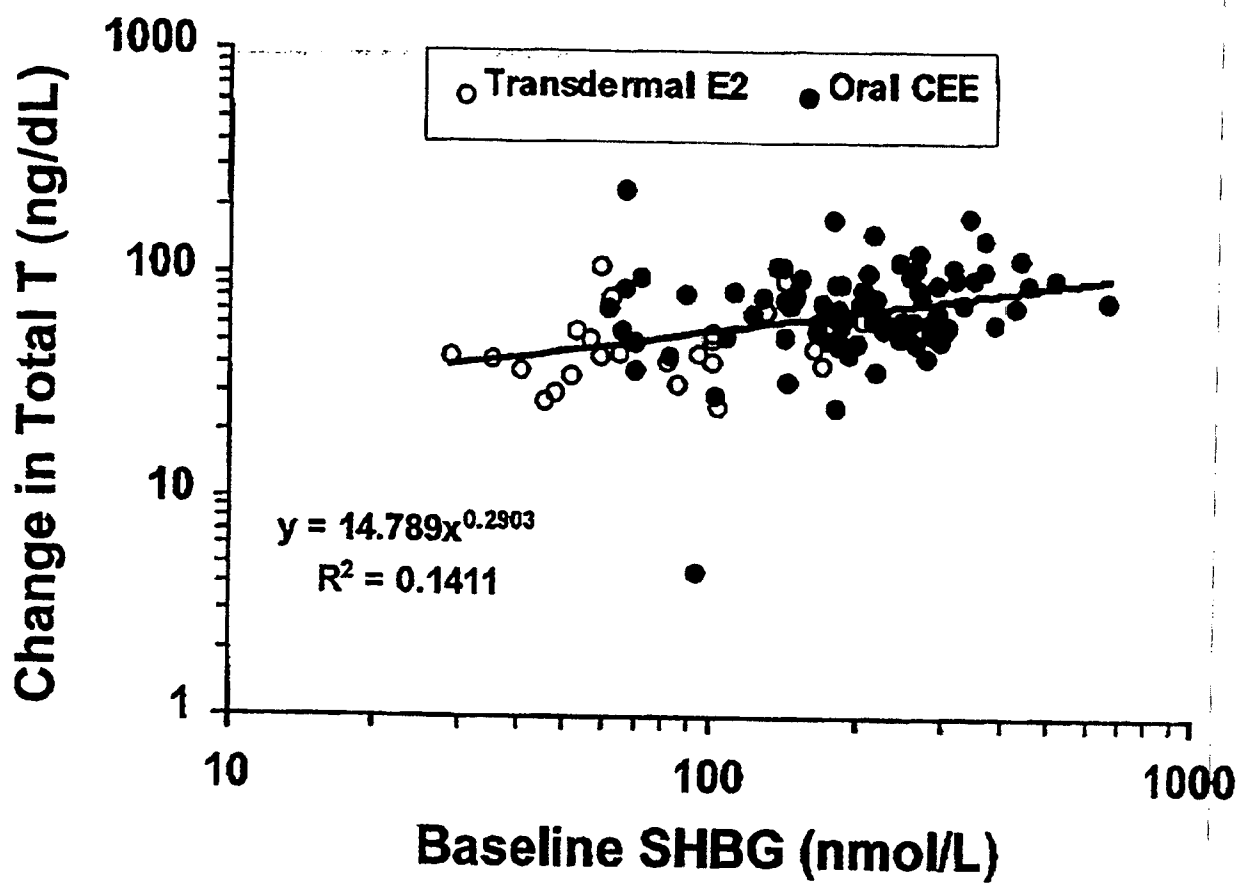


Figure 1

B2 63 125

557 00 45335103

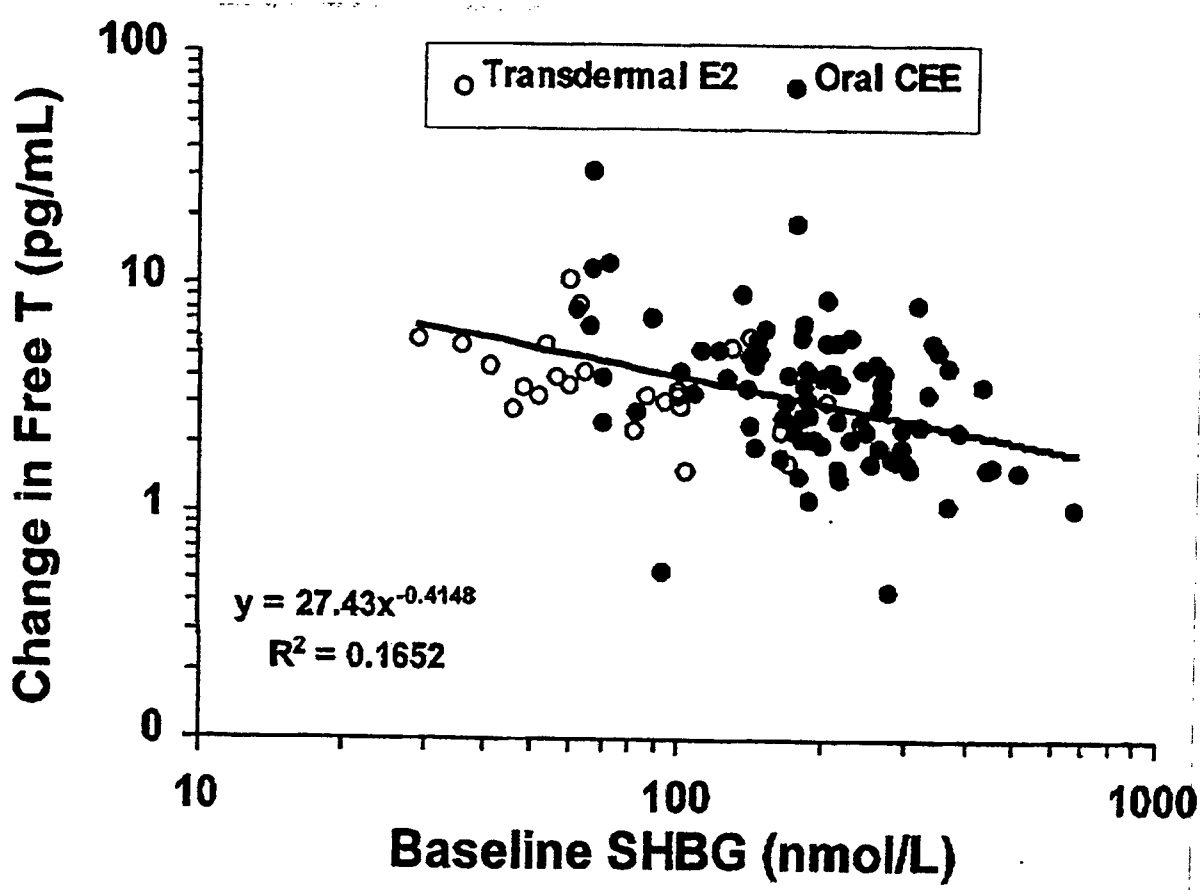


Figure 2

P-34365
B3 - 437

LOS ESTADOS UNIDOS DE AMÉRICA

A TODOS A QUIENES LOS PRESENTES DOCUMENTOS
PUDIERAN LLEGAR:

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS

Oficinas de Patentes y Marcas de los Estados Unidos

28 de junio de 2000

POR LA PRESENTE SE CERTIFICA QUE LA ANEXA AQUÍ ES UNA COPIA VERDADERA TOMADA DE LOS REGISTROS DE LA OFICINA DE PATENTES Y MARCAS DE LOS ESTADOS UNIDOS, DE LOS DOCUMENTOS DE LA SOLICITUD DE PATENTE ABAJO IDENTIFICADA QUE SATISFACE LOS REQUERIMIENTOS PARA SERLE OTORGADA UNA FECHA DE PRESENTACIÓN SEGÚN 35 USC 111.

NÚMERO DE SOLICITUD: 60/138,851
FECHA DE SOLICITUD: 11 de junio de 1999

Por la Autoridad del
COMISIONADO DE PATENTES Y MARCAS

(Hay firma ilegible)
T. LAWRENCE
Oficial de Certificaciones

Hay sello seco que dice:
OFICINA DE PATENTES Y MARCAS
ESTADOS UNIDOS DE AMÉRICA

Reivindicaciones

1. Un método para mejorar la salud de una mujer que comprende coadministrar cantidades efectivas de estrógeno y esteroides androgénicos, caracterizado porque el estrógeno se administra oralmente y dichos esteroides androgénicos se administran por medios parenterales.
2. Un método de acuerdo a la reivindicación 1 en donde dicho esteroide androgénico se administra en una dosis suficiente para mantener un nivel de esteroide androgénico libre en el suero equivalente a un nivel de testosterona libre en el suero de aproximadamente 0.5 a aproximadamente 15 pg/mL.
3. Un método de acuerdo a la reivindicación 2 en donde dicho esteroide androgénico se administra en una dosis suficiente para mantener un nivel de esteroide androgénico libre en el suero equivalente a un nivel de testosterona libre en el suero de aproximadamente 1 a aproximadamente 12 pg/mL.
4. Un método de acuerdo a la reivindicación 2 o 3 en donde dicho esteroide androgénico es un miembro seleccionado del grupo consistente de testosterona natural, ésteres de testosterona, metiltestosterona, androstenediona, adrenosterona, deshidroepiandrosterona, fluoximesterona, metandrostenolona, 17 α -metilnortestosterona, nandrolona y sus derivados, noretandrolona, dihidrotestosterona, oximetolona, estanozolol, etilestrenol, oxandrolona, bolasterona y mesterolona.

B5

67
139

5. Un método de acuerdo a la reivindicación 4 en donde dicho esteroide androgénico es un miembro seleccionado del grupo consistente de testosterona, ésteres de testosterona, dihidrotestosterona y metiltestosterona.
- 5 6. Un método de acuerdo a la reivindicación 5 en donde el esteroide androgénico es un miembro seleccionado del grupo consistente de testosterona, dihidrotestosterona y ésteres de testosterona.
7. Un método de acuerdo a la reivindicación 6 en donde dicho esteroide androgénico es testosterona.
- 10 8. Un método de acuerdo a la reivindicación 5 en donde el esteroide androgénico es metiltestosterona.
9. Un método de acuerdo a la reivindicación 5 en donde el esteroide androgénico es dihidrotestosterona.
10. Un método de acuerdo a la reivindicación 2 ó 3 en donde dicho
15 estrógeno administrado oralmente está en un intervalo de dosis equivalente a la respuesta a la dosificación obtenida al administrar estrógeno conjugado en un intervalo de dosis de entre 0.02 a 3.0 mg/día.
11. Un método de acuerdo a la reivindicación 10 en donde dicho
20 estrógeno administrado oralmente es seleccionado del grupo consistente de 17β -estradiol, α -estradiol, estrógeno conjugado, estrógenos esterificados, estradiol micronizado, estrógeno sulfato de sodio, etinil estradiol, estrona, otros esteroides estrogénicos y derivados y ésteres de los mismos.
- 25 12. Un método de acuerdo a la reivindicación 11 en donde dicho estrógeno administrado oralmente es un estrógeno conjugado.

136 58 40

13. Un método de acuerdo a la reivindicación 11 en donde dicho estrógeno administrado oralmente es un estrógeno esterificado.
14. Un método de acuerdo a la reivindicación 11 en donde dicho estrógeno administrado oralmente es un estradiol micronizado.
- 5 15. Un método de acuerdo a la reivindicación 2 ó 3 en donde dicha hormona estrógeno administrada oralmente está en la forma de un anticonceptivo oral.
- 10 16. Un método de acuerdo a la reivindicación 2 ó 3 en donde dicho mejoramiento de salud fisiológica es manifestado por uno ó más de los siguientes parámetros: restauración ó mejoría del deseo sexual, restauración ó mejoría de la estimulación a los órganos sexuales, restauración o mejoría de la habilidad para alcanzar orgasmos, restauración ó mejoría del placer en la actividad sexual, restauración ó mejoría de la energía vital y sentido de bienestar, mejoría en el
15 tono muscular, en la densidad mineral del hueso, en la piel y el cabello, y reducción en la inestabilidad vasomotora.
17. Un método de acuerdo a la reivindicación 2 ó 3 en donde la progesterona es administrada concomitantemente con la administración de estrógeno.
- 20 18. Un método de acuerdo a la reivindicación 2 ó 3 en donde el medio parenteral es seleccionado del grupo consistente de medios de liberación transdérmica, medios de administración tópica a la piel, medios de liberación sublingual, medios de liberación transbucal, medios de liberación transmucosal, implantes subdérmicos e
25 inyección intramuscular.

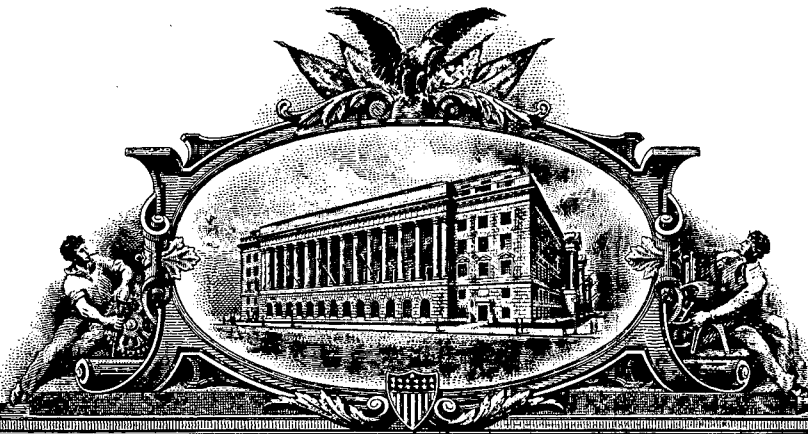
137 69 111

19. Un método de acuerdo a la reivindicación 18 en donde el medio parenteral es seleccionado del grupo consistente de medio de liberación transdérmica, inyección intramuscular, e implante subdérmico.
- 5 20. Un método de acuerdo a la reivindicación 19 en donde el medio parenteral es inyección intramuscular.
21. Un método de acuerdo a la reivindicación 19 en donde el medio parenteral es implante subdérmico.
22. Un método de acuerdo a la reivindicación 18 en donde el medio parenteral es un gel ó crema tópica.
- 10 23. Un método de acuerdo a la reivindicación 18 en donde el medio parenteral es un dispositivo transdérmico.
24. Un método de acuerdo a la reivindicación 23 en donde la inyección transdérmica es una matriz de tipo de dispositivo transdérmico.
- 15 25. Un método de mejoramiento de la salud en una mujer que recibe estrógeno oral en un régimen de estrógeno oral, que comprende administración de un esteroide androgénico por un medio parenteral para alcanzar un nivel equivalente a un nivel de testosterona libre en el suero desde 0.5 aproximadamente a 15 pg/mL aproximadamente.
- 20 26. Un método de acuerdo a la reivindicación 25 en donde el nivel de suero del esteroide androgénico es equivalente al nivel de suero de testosterona libre desde 3 aproximadamente a 12 pg/mL aproximadamente.
- 25 27. Un método de acuerdo a la reivindicación 26 en donde el nivel de suero del esteroide androgénico es equivalente al nivel de

138 HC
142

testosterona libre en el suero desde 5 aproximadamente a 10
pg/mL aproximadamente.

PA 268645



P. 343

B9

220
443

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

June 28, 2000

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: 60/138,854

FILING DATE: June 11, 1999



**By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS**

**T. LAWRENCE
Certifying Officer**

PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1.53 (b)(2).

Docket Number T7797	Type a plus sign (+) inside this box→	+
------------------------	--	---

INVENTOR(S)/APPLICANT(S)			
LAST NAME	FIRST NAME	MIDDLE INITIAL	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)
Mazer	Norman	A.	4641 S. Hunters Ridge Circle Salt Lake City, Utah 84124

TITLE OF THE INVENTION (280 characters max)
A METHOD OF COADMINISTERING ORAL ESTROGEN AND PARENTERAL ANDROGENIC STEROIDS TO WOMEN TO MAINTAIN A FUNCTIONAL LEVEL OF TESTOSTERONE IN WOMEN

CORRESPONDENCE ADDRESS
M. Wayne Western THORPE, NORTH & WESTERN, L.L.P. P.O. BOX 1219 JANDY

STATE	UTAH	ZIP CODE	84091-1219	COUNTRY	USA
-------	------	----------	------------	---------	-----

ENCLOSED APPLICATION PARTS (check all that apply)	
☒ Specification (Number of Pages) <u>57</u>	☐ Small Entity Status
☒ Drawing(s) (Number of Pages) <u>2</u>	☐ Other (specify)

METHOD OF PAYMENT (check one)		
☒ A check or money order is enclosed to cover the Provisional filing fees	PROVISIONAL FILING FEE AMOUNT (\$)	\$150.00
☒ The commissioner is hereby authorized to charge filing fees and credit Deposit Account Number: <u>20-0100</u>		
Deficiencies Only		

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are: _____

Respectfully submitted,

SIGNATURE M. Wayne Western Date 6/11/99 EXPRESS NO. EL163093559US

TYPED or PRINTED NAME M. Wayne Western REGISTRATION NO. 22,788
(if appropriate)

☒ Additional inventors are being named on separately numbered sheets attached hereto

PROVISIONAL APPLICATION FILING ONLY

Burden Hour Statement: This form is estimated to take 2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Office of Assistance Quality and Enhancement Division, Patent and Trademark Office, Washington, DC 20231 and to the Office of Information and Regulatory Affairs, Office of Management and Budget (Project 0651-00XX), Washington, DC 200503 DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS SENT TO: Commissioner of Patents and Trademarks, Washington, DC 20231

A/PROV 173
144
140

JC541 U.S. PTO
60/138854

06/11/99

JC674 U.S. PTO

PROVISIONAL APPLICATION COVER SHEET (CONTINUED)

141
74
145

ADDITIONAL INVENTOR(s)/APPLICANT(s)			
LAST NAME	FIRST NAME	MIDDLE INITIAL	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)
Rosario-Jansen	Theresa		6773 Little River Lane Loveland, OH 45140

H:\Jeffries\Provisional Application Cover Sheet for T7797.wpd

1412 75
1410

5 EXPRESS LABEL NO. EL163093559US

PATENT APPLICATION

ATTORNEY DOCKET T7797

0 A METHOD OF COADMINISTERING ORAL ESTROGEN AND PARENTERAL
ANDROGENIC STEROIDS TO WOMEN TO MAINTAIN A FUNCTIONAL LEVEL
OF TESTOSTERONE IN WOMEN

TECHNICAL FIELD

5 This invention relates to a method of alleviating signs
and physiological symptoms attributable to the deficiency or
imbalance of estrogen and androgenic hormones in females.
Particularly, it is directed to methods of administration of
parenteral androgenic steroids to women who are taking
20 estrogen orally, to maintain a functional level of
testosterone in women, even though that level may be outside
what might be considered normal physiological serum levels
according to published standards. Such level may be
necessary to be functional to alleviate various signs and

RPE, NORTH & WESTERN, LLP
Box 1219
v, Utah 8491-1219
hone (801) 566-6633

14B 76 147

5 symptoms attributable to the deficiency or imbalance of
estrogen and androgenic hormones, thus providing to females
an optimal effect on sexual function, energy and sense of
well-being.

10 BACKGROUND

15 There are a variety of conditions in which women
express hormonal imbalance. Women who are menopausal,
either naturally or as a result of ovarian failure or loss
(e.g., secondary to hysterectomy, surgical oophorectomy or
chemotherapy) frequently develop estrogen and testosterone
deficiencies with their attendant undesirable effects. In
these women, the need for estrogen replacement therapy (ERT)
is determined by symptoms developed by a woman or, in some
cases, by a blood test to determine serum estrogen levels.
20 Another situation in which women may express hormonal
imbalance is when they are receiving estrogen-containing
oral contraceptives. By suppressing ovarian function, oral
contraceptives diminish testosterone production resulting in
androgen deficiency in these pre-menopausal women.

144 77 148

5 Use of oral estrogens causes an increase in a woman's
sex hormone binding globulin (SHBG). SHBG is a protein
produced by the liver that tightly binds estrogen and
testosterone in the blood. In its bound state, the sex
hormone is not available to exert its biological action at
0 receptors in target tissues. Not only is SHBG-bound hormone
not available to bind to receptors, it is also not available
for metabolic clearance. Hence, women receiving oral
estrogen therapy can become functionally testosterone
deficient for two reasons. First, estrogen administration
lowers or suppresses the pituitary luteinizing hormone (LH),
which stimulates the ovarian production of testosterone.
Second, by increasing SHBG levels, the availability of
testosterone is diminished or deficient.

20 In contrast to the effects of oral estrogen
administration, SHBG does not increase when estrogens are
provided by non-oral delivery routes, such as transdermal
delivery of estrogens. A comparison of mean SHBG levels in
oophorectomized women receiving either no estrogen
replacement therapy, transdermal estradiol (0.1 mg/day) or

145 78
119

oral conjugated equine estrogen (1.25 mg/day) is given in Table 1.

Table 1

Hormone data (mean $\pm$ SEM) in three groups of surgically menopausal women evaluated in pharmacokinetic studies of testosterone matrix patches. Each woman received 300 mcg/day of testosterone delivered transdermally from a matrix patch.

Hormone (unit)	No ERT n=19	Transdermal E2 (0.1 mg/day) n=12	Oral CEE (1.25 mg/day) n=13
Baseline SHBG Levels (nmol/L)	85.6 $\pm$ 9.6	90.8 $\pm$ 12.9	226.3 $\pm$ 13.5
Change in total T (ng/dl)	57.2 $\pm$ 4.4	53.6 $\pm$ 7.2	70.8 $\pm$ 9.6
Change in Free T (pg/mL)	4.60 $\pm$ 0.40	4.20 $\pm$ 0.70	2.56 $\pm$ 0.30

In the above table:

E2 is estradiol
T is testosterone
CEE is conjugated equine estrogens

As shown in Table 1, SHBG levels in the oral estrogen group are approximately 2.5-fold larger than the other groups and exceed the upper limits of the normal range. In

146 74 150
5 the transdermal estradiol group, SHBG levels are comparable
to the untreated patients. The differential effects of oral
and transdermal estrogen on SHBG levels are believed to
result from the hepatic first-pass effect of the oral
estrogen administration, which either raises hepatic SHBG
10 production or diminishes hepatic clearance of SHBG.

As a corollary to the differential effects of oral and
transdermal estrogen on SHBG levels, the levels of total and
free (unbound) testosterone that are attained with
parenteral testosterone administration also differ. As shown
15 in Table 1, in the case of transdermal testosterone
administration at the dosage of 300 mcg/day, the changes in
total testosterone levels are approximately 30% larger for
the oral estrogen group than the other groups. In contrast,
the changes in free testosterone levels are approximately
20 40% lower for the oral estrogen group than the other groups.
It is generally recognized that both the free testosterone
and the albumin-bound fraction of testosterone are
bioavailable to interact at receptors, and the sum of these
are termed the "bioavailable testosterone" fraction.

ORPE, NORTH & WESTERN, LLP

Box 1219

ty, Utah 8491-1219

phone (801) 566-6633

5 Herein, we will use the terminology "free" testosterone to
connote the functional level of testosterone since it is the
more commonly measured serum component.

10 The greater increase in total testosterone levels
associated with oral estrogen administration is presumably
due to the decrease in testosterone clearance that results
from the elevation in SHBG levels and the corresponding
reduction in the free fraction of testosterone. Conversely,
the smaller increase in free testosterone levels with oral
estrogen administrations indicates that the reduction in the
free fraction exceeds the reduction in testosterone
clearance.

20 The latter is a new and unexpected finding that could
not have been predicted from earlier studies of testosterone
clearance. As a general consequence of these phenomena one
would expect that for a given regimen of parenteral
testosterone delivery to women, total testosterone will
increase while free testosterone will decrease as a function
of increasing SHBG levels. This finding is illustrated with
individual patient data compiled from three studies in which

148
981
152

5 women on oral or transdermal estrogen received transdermal
testosterone at a nominal delivery rate of 300 mcg/day (see
Figures 1 and 2). As depicted on logarithmic scales,
changes in total T increased significantly, while changes in
free T decreased significantly as a function of SHBG level.

10 From the perspective of achieving the beneficial
effects of parenteral testosterone therapy in testosterone-
deficient women concomitantly receiving oral estrogen, these
data have three key implications:

15 First, the total testosterone levels attained during
treatment may substantially exceed the upper limit of the
normal physiological range of testosterone levels, as
determined in women with normal SHBG levels. Second, since
free testosterone levels are believed to exert the
biological effects of testosterone on target tissues, they
20 are preferable to the total testosterone in monitoring
therapy, and should not substantially exceed the upper limit
of the normal range in most circumstances. Third, for women
with inordinate elevations in SHBG, the total parenteral
delivery rate of testosterone necessary to achieve

149 82 155

5 beneficial and safe effects may exceed the previously
defined ranges such as described by Ebert, et al. in U.S.
Patent 5,460,820. This range was reported to be 50-500
mcg/day for testosterone from a transdermal patch dosage
form, with or without the concomitant administration of
10 estradiol from the same patch. The present invention is
mainly directed to total testosterone levels. Two copending
applications, filed under Thorpe, North & Western docket
numbers T7798 and T7118 on even date herewith, are directed
to free testosterone levels and delivery rates of
15 testosterone associated with SHBG elevation resulting from
orally administered estrogens.

20 In women who have a uterus, it is imperative that they
receive a concomitant progesterone, as unopposed estrogen
use is associated with endometrial hyperplasia which can
lead to uterine cancer. Progesterone and synthetic analogs
thereof may prevent this unwanted estrogen effect.

Progestins are also utilized in oral contraceptives.

The oral administration of estrogen to females,
particularly postmenopausal or oophorectomized women (i.e.

150 83 154

5 women who have had one or both of their ovaries removed), is
common. In the context of estrogen replacement therapy,
researchers and medical practitioners have long recognized
the need to administer estrogen to make up for or supplement
the production of estrogen in women who have need thereof.
10 Conjugated estrogens, in dosage ranges of about 0.02 to 3.0
mg/day (or the equivalent of other estrogens, such as
micronized estradiol or ethinyl estradiol, to obtain the
same response) are orally administered to supplement
decreasing or lack of ovarian function. Synthetic progestin,
such as norethindronl acetate, can be administered orally or
transdermally to prevent endometrial hyperplasia. To control
conception in the case of oral contraceptives, ethinyl
estradiol is administered in a regimen known in the art.

20 However, it is recognized that merely supplementing
estrogen is not sufficient to maintain a woman's health and
well being. Many women continue to experience symptoms such
as loss of sexual desire, diminished vital energy, a
diminished sense of well-being, bone loss that is not

151 84 155

5 completely ameliorated by estrogen treatment, and loss of
muscle strength and mass.

10 In the female, androgens are produced by the adrenal
glands and ovaries in small amounts and have multiple
effects on a variety of target tissues, e.g. muscle, bone,
15 skin, brain, and genitalia. Recent research has shown that
androgens, and particularly testosterone, contribute
substantially to bone density, as well as to muscle tone and
certain cognitive abilities. Several reports in the
literature establish the beneficial effects of androgen
20 therapy on sexual function.

Ebert, et al., U.S. Patent 5,460,820, in one aspect,
teaches a composition and method for administering
testosterone transdermally via a patch delivery system.
However, in many instances it may be more advisable to
administer estrogen orally to a woman. Further, it may be
advantageous to administer androgens by other parenteral
routes, depending on the individual patient's
characteristics and preferences. It is recognized that
parenteral delivery of androgens is safer to the liver and

152 85
156

5 provides more sustained delivery than oral routes since the first pass metabolism effects are bypassed. On the other hand, oral delivery of estrogens allows for an improved serum lipid profile.

10 Ebert, et al., supra, is drawn to a method for maintaining total testosterone serum blood levels in a "physiological range" of between about 15 to 80 ng/dL by means of transdermally administering about 50 to 500 mcg/day of testosterone from a testosterone matrix transdermal delivery system. Other publications indicate the physiological total testosterone serum range may vary somewhat, but is generally within or close to the above stated parameters. However, it has been discovered that the above-stated total testosterone serum levels for females may not be an accurate indicator of functional testosterone levels in women receiving oral estrogen therapy. Oral estrogens tend to decrease or suppress androgenic steroid secretion and increase the production of sex-hormone binding globulin (SHBG). Also, as discussed above, SHBG binds testosterone, thereby decreasing its bioavailability to

153 86
157

5 target tissues. Therefore, in order for the female receiving
oral estrogen to have adequate testosterone to obtain a
desired physiological response, it may be necessary that the
total testosterone serum level be greater than the published
physiological ranges.

10 In view of the above, it would be desirable to provide
compositions and methods for their administration that would
enable women exhibiting symptoms attributable to the
deficiency or imbalance of estrogen and androgenic hormones
to take supplemental amounts of oral estrogen and parenteral
androgenic steroids in such a manner as to maintain a
balanced, functional serum level of estrogen and androgenic
hormones. Such functional level of androgenic hormones in
females promotes the return of sexual health and activity,
feelings of well-being, cardiovascular and coronary health,
decreases breast tenderness, maximizes muscle tone and
inhibits bone loss, decreases vasomotor instability, and may
enhance certain cognitive abilities. The present invention
is drawn to attaining these goals by administration of

154 87 158

5 parenteral androgenic steroids to women receiving oral
estrogen.

SUMMARY OF THE INVENTION

10 One object of the present invention is to provide a
method of improving health in a woman comprising
coadministering effective amounts of estrogen and androgenic
steroids characterized in that the estrogen is administered
orally and the androgenic steroid is administered
parenterally. In a related aspect, an object of the
invention is to provide a method of improving health in a
15 woman receiving estrogen orally in accordance with a regimen
(e.g., ERT or oral contraceptive), the method comprising
administering to the woman an androgen steroid parenterally.
Estrogen, based on conjugated estrogen, is typically
20 administered orally in a dosage range of between about 0.3
to 3.0 mg/day in women receiving ERT. In an oral
contraceptive context, estrogen is typically administered in
the form of ethinyl estradiol in a dosage range of between
about 0.02 to 0.035 mg/day. The parenteral administration

ORPE, NORTH & WESTERN, LLP

2. Box 1219
Idy, Utah 8491-1219
ephone (801) 566-6633

155 28 759

5 of androgenic steroid is in a dosage range that is
sufficient to maintain the total testosterone serum levels
in the woman, based on native testosterone, in a range of
between about 15 and 400 ng/dL, preferably in a range of
between about 85 and about 300 ng/dL, most preferably in a
10 range of between about 90 and about 250 ng/dL. As will be
discussed below, because of the surprising effect of SHBG in
women receiving oral estrogen, the levels of delivered
testosterone and total serum testosterone required to obtain
the desired FT levels is higher than previously expected.
15 Dosage forms of other estrogens, for example ethinyl
estradiol, and other androgens, for example, methyl
testosterone, are formulated to yield an equivalent response
to conjugated estrogen and testosterone.

20 Another object of the present invention is to improve
health in a woman comprising coadministering effective
amounts of oral estrogen and parenteral androgenic steroids,
wherein the improvement of health is manifest by one or more
of the following parameters: restoration or enhancement of
sexual desire, restoration or enhancement of stimulation to

156

489
460

5 sexual organs, restored or enhanced ability to achieve
orgasm, restoration or enhancement in pleasure in sexual
activity, restoration or enhancement of vital energy and
sense of well-being, improvement or enhancement in muscle
tone, skin and hair appearance, restoration or improvement
10 in cognition, increased bone mineral density, improvement in
blood lipids, improvement in cardiovascular tone and
responsivity, and reduction in vasomotor instability.

These and other objects are accomplished by providing a
method of improving health in a woman comprising
coadministering effective amounts of estrogen and androgenic
steroids characterized in that said estrogen is administered
orally and said androgenic steroid is administered
parenterally.

Estrogen, based on conjugated estrogen, is administered
orally in a dosage range of between about 0.02 to 3.0
mg/day, the specific dosage being dependent on the nature of
the estrogen background (e.g., ERT or oral contraceptive),
as well as individual patient needs. The androgenic steroid
is administered in a dosage range sufficient for achieving a

157 90 161

5 serum level, based on total testosterone, of about 15-400
ng/dL and preferably 15-250 ng/dL. Dosage forms of other
estrogens and androgens are formulated to yield an
equivalent response to conjugated estrogen and testosterone.

Any functional androgenic steroid may be administered.
10 Representative androgenic steroids are members selected from
the group consisting of native testosterone, testosterone
esters, methyltestosterone and other 17-alkylated versions,
androstenedione, adrenosterone, dehydroepiandrosterone,
fluoxymesterone, methandrostenolone, 17 α -
5 methylnortestosterone, norethandrolone, dihydrotestosterone,
oxymetholone, nandrolone and its derivatives, stanozolol,
ethylestrenol, oxandrolone, bolasterone and mesterolone.
Preferably, the androgenic steroid is a member selected from
the group consisting of testosterone, testosterone esters
20 and methyltestosterone. Most preferably, the androgenic
steroid is selected from the group consisting of
testosterone, dihydrotestosterone, methyltestosterone and
testosterone esters such as testosterone cypionate,

158 91/102

5 testosterone enanthate, testosterone phenylacetate, and
testosterone propionate.

The preferred means for parenterally administering the
androgenic steroid is transdermal delivery. For transdermal
delivery, preferred are the matrix or container type of
10 patches. Matrix type patches are most preferred.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows change in total testosterone level versus
baseline SHBG level during application of transdermal
testosterone patch (300 mcg/day nominal delivery) to
45 patients concomitantly receiving transdermal estradiol or
oral conjugated equine estrogens. Equation describes power
law fit to data with corresponding R-square value.

FIG. 2 shows the change in free testosterone level
20 versus baseline SHBG level during application of transdermal
testosterone patch (300 mcg/day nominal delivery) to
patients concomitantly receiving transdermal estradiol or
oral conjugated equine estrogens. Equation describes power
law fit to data with corresponding R-square value.

5

159 92 163

DETAILED DESCRIPTION OF THE INVENTION

10 The present invention relates to methods for
coadministering oral estrogen and parenteral androgenic
steroids, in effective amounts, to women who are in need of
supplementation, such as women exhibiting symptoms
attributable to the deficiency or imbalance of estrogen and
androgenic hormones due to menopause and/or natural aging or
as a result of hysterectomy, oophorectomy or ovarian failure
(e.g., consequent to chemotherapy), or adrenal
insufficiency.

20 The invention relates to a method of coadministration
of oral estrogen and parenteral androgenic steroids to women
in need to alleviate symptoms attributable to the deficiency
or imbalance of estrogen and androgenic hormones and to
provide optimal effects on health, sexual function and well-
being. With respect to androgenic hormones, the method will
comprise administering androgen at levels sufficient to
provide total testosterone levels of from about 15 to about
400 ng/dl. Typically, to achieve the desired effect, the

160
164

5 total serum testosterone levels will be from about 85 to
about 300 ng/dl, more typically from about 90 to about 250
ng/dl, and most typically from about 90 to about 200 ng/dl.
As indicated, the amount of testosterone delivered, and in
particular the total serum testosterone levels, required to
10 achieve the desired results are generally higher than
previously expected, due to the elevated SHBG levels in
women receiving oral estrogen.

Before the present methods of improving health in a
woman are disclosed and described, it is to be understood
that this invention is not limited to the particular process
15 steps and materials disclosed herein as such process steps
and materials may vary somewhat. It is also to be
understood that the terminology employed herein is used for
the purpose of describing particular embodiments only and is
not intended to be limiting since the scope of the present
20 invention will be limited only by the appended claims and
equivalents thereof.

161
44
465

5 In describing and claiming the present invention, the following terminology will be used in accordance with the definition set out below.

10 As used within the context of this invention, the term "coadministration" means administration of multiple active substances to one individual, either simultaneously or sequentially. Thus, the term includes any situation in which women are receiving oral estrogen and parenteral androgen. The term does not imply that the estrogen and androgen actives have to be administered at the same time. Rather, as long as a woman is receiving estrogen orally, administration of parenteral androgen to maintain the desired free testosterone levels will be within the present definition for "coadministration". For example, parenteral administration of androgenic steroids to an individual who has previously been placed on oral estrogen therapy is within the meaning of "coadministration" in the present application. Thus, it is clear that the estrogen and the androgen actives need not be provided in a single product to be "coadministered".

162 95 466

5 As used within the context of this invention, the terms
"androgenic steroid", "testosterone agent" or "testosterone"
(when used generically), must be taken in context and are
generally meant to encompass any androgenic steroid that is
functional in reducing signs and symptoms of testosterone
10 deficiency in females. Members selected from the group
consisting of native testosterone, testosterone esters,
methyltestosterone and other 17-alkylated versions, methyl
testosterone esters, androstenedione, adrenosterone,
dehydroepiandrosterone, fluoxymesterone, methandrostenolone,
15 17 α -methylnortestosterone, norethandrolone,
dihydrotestosterone, oxymetholone, nandrolone and its
derivatives, stanozolol, ethylestrenol, oxandrolone,
bolasterone and mesterolone are representative of androgenic
steroids. Of this group testosterone, dihydrotestosterone
20 testosterone esters and methyltestosterone are preferred.
Representative esters include the propionate, phenylacetate,
enanthate and cypionate esters of testosterone.

The term "parenteral" refers to any route of
administration other than the gastrointestinal tract and can

163 90 167

5 include, but is not limited to: intramuscular injections;
subcutaneous injections or implants; transdermal, e.g.,
patch, lotion, cream, gels, sprays; transmucosal, e.g.,
buccal, sublingual, vaginal and rectal.

10 The terms "estrogen", "estrin" or "estrogenic hormone"
(when used generically) refers to any substance, natural or
synthetic, that exerts biological effects characteristic of
estrogenic hormones such as estradiol and equivalents
thereof. Members selected from the group consisting of 17 β -
estradiol, α -estradiol, conjugated estrogens, esterified
estrogens, micronized estradiol, sodium estrogen sulfate,
ethinyl estradiol, estrone, and other estrogenic steroids
and derivatives and esters thereof are representative of
estrogens. Representative esters include estradiol-3,17-
diacetate, estradiol-3-acetate, estradiol-17-acetate,
estradiol-3,17-divalerate, estradiol-3-valerate, estradiol-
17-valerate. Of this group 17 β -estradiol, and corresponding
pivalate, propionate, cypionate, benzoate, and like esters
are preferred.

HORPE, NORTH & WESTERN, LLP

O. Box 1219

ndy, Utah 8491-1219

elephone (801) 566-6633

161 168

5 The term "oral estrogens" refers to any estrogenic
hormone which is in a dosage form suitable for oral
administration. Conjugated estrogens, esterified estrogens
and micronized estradiol are the most preferred in an ERT
context. Commercially available oral products of estrogens
10 include conjugated estrogens available under the trade name
Premarin® from Wyeth-Ayerst Laboratories, and esterified
estrogens available under the trade name Estratab® from
Solvay Pharmaceuticals. Ethinyl estradiol is the most
preferred estrogen in oral contraceptives.

15 The term "progesterone" refers to native progesterone,
medroxyprogesteroneacetate, norethindrone, and norethindrone
acetate and the equivalents thereof.

20 As used herein the terms "serum level", "blood level",
"total blood level", and "endogenous serum level" include
the serum levels of total testosterone or estradiol,
including protein-bound and free form of serum testosterone.
According to published standards, the total testosterone
range in normal, healthy women who are not receiving drugs
that alter SHBG is about 15-80 ng/dL; whereas for estradiol

165
28
169

5 it is about 25-200 pg/mL. In the case of the derivatives of
testosterone or estradiol, amounts that provide equivalent
androgenic or estrogenic activity, as the case may be, to
the natural hormones are intended.

10 The term "serum total testosterone" refers to the value
obtained when testosterone is measured by an appropriate
radioimmunoassay (RIA). It is generally accepted that the
total testosterone fraction consists mainly of three
components: (1) unbound, or free testosterone; (2) albumin-
bound testosterone; and (3) SHBG-bound testosterone. Either
free or bioavailable testosterone, i.e. the concentration of
non-SHBG bound testosterone, can be indicative of the
functional level of testosterone in the blood. Total serum
testosterone can be measured by RIA at a clinical
laboratory, using standard techniques, for example, RIA
procedure used by Endocrine Sciences, Inc. (Calabasas Hill,
20 CA). According to such procedure, serum samples are
extracted with hexane:ethyl acetate. The extract is then
applied to Al₂O₃ micro columns. The columns are washed with
hexane containing 0.55% ethanol. Finally, testosterone is

166

99
170

5 specifically eluted using hexane containing 1.4% ethanol.
Duplicate aliquots are then taken for RIA. Purified samples
are incubated with an antibody made to a testosterone-3-
oxime-BSA conjugate. Free and antibody-bound testosterone
in each sample is calculated from a curve generated by
10 purified testosterone standards. Sensitivity of the method
is 3 ng/dL when a normal 0.5 ml serum aliquot is used.

The term "serum bioavailable testosterone" refers to
the fraction of testosterone in the serum that is not bound
by SHBG, and can be measured by standard commercial
15 laboratories, for example, the following procedure at
Endocrine Sciences, Inc. Sample preparation begins with an
ammonium sulfate precipitation of the SHBG-bound
testosterone in the serum sample. Then, the amount of
testosterone remaining in the sample is determined using the
20 total testosterone remaining in the sample, using the total
testosterone determination.

The term "serum free testosterone" refers to the
fraction of testosterone in the serum that is not protein
bound and can be measured by standard commercial

167 100 121

laboratories, for example, the following procedure at
Endocrine Sciences, Inc. Serum is placed inside a
semipermeable dialysis bag and dialyzed against a buffer
containing tritium labeled testosterone outside the dialysis
bag. The percent free testosterone is calculated from the
ratio of radioactivity outside the bag versus inside the
bag. This percent free testosterone, multiplied by the
total testosterone in the serum and corrected for units,
results in the concentration of free testosterone in the
serum. Protein levels are checked in the dialysate to be
sure the dialysis bag has not leaked. The minimum
reportable free fraction is 0.1 percent free.

As used herein, "SHBG" is the protein sex hormone
binding globulin in the serum that can be measured by a
commercial laboratory standard method, e.g., the
immunoradiometric assay from Endocrine Sciences, Inc. A
monoclonal antibody made to human SHBG is coated onto
plastic beads. The sample and a different SHBG monoclonal
antibody, which is labeled with ¹²⁵I, are incubated overnight
with the antibody coated bead. SHBG in the sample and the

168

101
172

5 standard form BEAD-ANTIBODY-SHBG-ANTIBODY ¹²⁵I sandwiched
complexes, attaching ¹²⁵I lable to the beads. The beads are
then washed to removed unbound label, and counted.

As used herein, "transdermal" or "percutaneous"
delivery means delivery of an androgenic steroid by passage
10 into and through the skin tissue. Terms "skin," "derma,"
"epidermis," and the like shall be used interchangeably
unless specifically stated otherwise.

The term "diffusional communication" intends that when
a transdermal androgenic steroid device of the invention is
placed on the skin of a woman, there is a direct or indirect
diffusional pathway by which the androgenic steroid can
migrate from the hormone-containing elements of the device
to the skin of the wearer.

The terms "delivery system," "patches" or any similar
terminology mean a matrix or container type of delivery
device which is used to transdermally deliver defined doses
of androgenic steroids, over a specific application period.
A preferred patch for administering androgen steroid in
accordance with this invention is a matrix-type patch which

169
102
173

comprises an occlusive backing that is impermeable to the androgen steroids and defines the face or top surface of the patch and a solid or semisolid matrix layer comprised of a homogeneous blend of the hormone, a polymeric pressure sensitive adhesive carrier, and optionally one or more skin permeation enhancers. Matrix patches are known in the art of transdermal drug delivery. Examples, without limitation, of transdermal patches are those described or referred to in U.S Patent Nos. 5,122,383 and 5,460,820 and are hereby incorporated by reference.

Several parenteral modes of delivery may be employed for the androgenic compound. These include: transdermal delivery via patch, gel, cream, ointment, film, or other means of application to the skin; transmucosal routes, including sublingual or buccal routes, which afford more long lasting blood levels than oral delivery; intramuscular injection; and subdermal implants. The preferred means for parenteral administrations are by the transdermal route, intramuscular injection, or subdermal implant. The most preferred means for transdermally administering the

170 103 174

5 androgenic steroids are the matrix or container type of patches. Of these systems, the matrix type patches are most preferred.

For transdermal administration, skin permeation enhancer(s) may be included in the formulations to enhance the level of skin flux of the hormone. Examples, without limitation, of skin permeation enhancers that may be used in, e.g., matrix patches, are those described or referred to in U.S. Patent Nos 5,122,383 and 5,153,997, the disclosures of which as they relate to skin permeation enhancers are incorporated by reference. The enhancer will usually constitute 1 to 20 wt % of the adhesive carrier forming the matrix.

Patches for transdermal delivery of androgen steroids may be manufactured by conventional techniques used in the art of transdermal drug delivery devices. For instance, the hormones, carrier, and enhancers may be mixed in the desired proportions to form a homogeneous mixture and then cast or otherwise applied to a backing layer by lamination to a release liner layer.

Obviously, the need for supplementing estrogen and androgenic steroids should be determined by a physician or other health care professional based on monitoring signs and symptoms of estrogen and testosterone deficiency. Not every female will exhibit the same symptoms and it is possible that testosterone levels might even be within physiological ranges but, based on other factors, for example, increased SHBG, testosterone deficiency may still be diagnosed. Such symptoms might include, but not be limited to, global loss of sexual desire, decreased sensitivity to sexual stimulation in the nipples and in the clitoris, decreased arousability and capacity for orgasm, diminished vital energy and sense of well-being, and loss of muscle tone. Some women also notice other symptoms such as thinning and loss of pubic hair, genital atrophy not responsive to estrogen, dry and brittle scalp hair, and dry skin. Other symptoms, while less documented, include increased risk for cardiovascular and coronary heart disease, decreased cognitive abilities and dry eyes in patients suffering from Sjogren's syndrome. Women who are receiving oral estrogens

HORPE, NORTH & WESTERN, LLP
P. O. Box 1219
Candy, Utah 8491-1219
Telephone (801) 566-6633

172-105
176

5 can also benefit from androgen therapy since it may reduce
the breast tenderness that can occur with estrogen usage.
Owing to the known breast tissue antiproliferative effects,
androgens may also reduce the excess risk of breast cancer
associated with estrogen use.

10 It is therefore highly desirable, if not imperative,
that testosterone supplementation for a female patient be
based on a diagnosis by a physician who prescribes the mode
of application, dosage and duration of treatment.

As described above, one aspect of the present invention
is to provide a method of improving health in a woman
comprising coadministering effective amounts of estrogen and
androgenic steroids characterized in that the estrogen is
administered orally and the androgenic steroid is
administered transdermally. Estrogen, based on conjugated
estrogen, is administered orally in a dosage range of
between about 0.02 to 3.0 mg/day. For some women,
particularly those women who are not in need of control of
vasomotor symptoms, the frequency of dosing may be less
often than once per day, which, may still maintain benefits

123 106 177

5 for bone health. In the case of oral contraceptive use,
ethinyl estradiol is typically given cyclically in a 21 day
on, 7 day placebo regimen.

10 The oral administration of estrogens increases the
levels of SHBG, which in turn decreases the bioavailable or
free testosterone level. Since additionally, SHBG-bound
androgen is not as readily available to metabolizing
enzymes, metabolic clearance rates are decreased. However,
the net effect, which was discovered experimentally, is that
the oral estrogens effectively decrease the levels of
circulating functional testosterone(i.e. free or
bioavailable testosterone levels) in a woman's body via an
increase in the SHBG, since the steady state levels of free
or bioavailable testosterone are affected more strongly by
the binding to SHBG rather than reduced metabolic clearance
rates. This has not been previously appreciated and is the
basis for achieving supra-physiological levels of total
testosterone in some women receiving oral estrogen therapy.

The administration of androgenic steroid is in a dosage
range equivalent to the dose response that results in a

174 107
178

5 serum level of about 15-400 ng/dL of testosterone, the exact
value varying from patient to patient, and depending on the
methodology used. The range 15-400 ng/dL corresponds to
laboratory values obtained using a radioimmunoassay (RIA).
When SHBG levels are high due to oral administration of
10 estrogens, the androgen will typically be administered to
achieve blood ranges of between about 85 and 300 ng/dL total
testosterone. More typically, the androgen will be
administered to achieve blood ranges of between about 90 and
250 ng/dL total testosterone.

15 Synthetic androgens serum level may be measured using
gas chromatography combined with mass spectrometry. Those
skilled in the art will be able to utilize such analytical
methods to determine the serum levels of these synthetic
androgens.

20 Serum or total testosterone, as determined by analysis
of blood or other body fluid, will generally refer to native
testosterone. Based on the above dosages and laboratory
tests, one skilled in the art can readily determine what
amount of a particular androgenic steroid or testosterone

175 108 179

5 derivative to administer to achieve the desired serum
levels. What is important is that the dose of the
androgenic steroid or testosterone derivative must be
sufficient to overcome, or at least alleviate, the
deficiency being monitored or treated, without administering
10 too great a dosage. However, it is an object of this
invention to provide a method of treating testosterone
deficiencies in women who are taking oral dosages of
estrogen to alleviate physiological symptoms attributable to
the deficiency or imbalance of estrogen and androgenic
15 hormones and to provide optimal effects on health, sexual
function, and well-being. Further, since the oral estrogen
increases the amount of SHBG, this invention relates to a
method for overcoming this effect. Due to the natural
variation in hormone sensitivity, the exact dosage is not as
20 critical as is the obtaining of the resultant physiological
response for that particular patient, which can correspond
to a total testosterone serum level of about 15-400 ng/dL.
What is more important, due to the high SHBG environment, is
that this level corresponds to an effective level of

176 109 180

5 biologically active testosterone component. To achieve this
level, higher total testosterone levels may be required than
previously thought.

10 Too high a dosage of testosterone or other androgen
steroids, or application of a dosage for too long a period
of time may be manifest by symptoms of testosterone excess,
i.e. irritability, clitoral enlargement, increased facial
hair and lowering of the voice. The incidence of side
effects depends somewhat on the woman's own sensitivity to
androgens, but is also dependent on the level of
bioavailable or free testosterone at the target tissue.
Owing to the potential for side effects, the lowest
concentration that can bring about the desired effects is
preferred. Generally speaking, the guidelines contained in
the present invention should yield a satisfactory safety
20 profile.

While the invention encompasses the utilization of
testosterone, testosterone esters and methyltestosterone, it
may be beneficial to utilize methyltestosterone or similarly
non-aromatizable androgens, such as dihydrotestosterone,

SECRET, DE 14 1966

177-110
181

5 when it is preferred that estradiol levels be maintained at
a low level. Methyltestosterone does not tend to aromatize
in situ into estradiol, whereas small amounts of
testosterone may be converted to estradiol. Use of
methyltestosterone is of particular value, for example, in
10 women who develop testosterone deficiency as a result of
ovarian failure following chemotherapy for breast cancer and
who need to keep their estrogen levels as low as possible.
However, while the following examples primarily illustrate
the use of testosterone, testosterone esters and
methyltestosterone, such are not intended to be a limitation
on the invention as other androgenic steroids may also be
utilized to bring about the desired results but may need to
be monitored more carefully.

20 In the embodiments exemplified in the following
examples, a dosage sufficient to provide a serum level of
about 15-400 ng/dL, of testosterone is administered to a
woman receiving oral estrogen in an ERT regimen. In other
words, the androgenic steroid is administered in a dosage
range equivalent to the dosage response obtained from

176 192

5 administering sufficient native testosterone or a
testosterone ester to produce a serum level of about 15-400
ng/dL, testosterone and obtain the desired response in the
woman to whom it is administered. The concentration most
appropriate for a particular woman on oral ERT or oral
10 contraceptives can be determined empirically, e.g., by
varying the delivery dosage and assessing the resulting
response as it may relate to indications such as sexual
function and general sense of well being. Depending on the
SHBG concentration, as affected by the oral ERT, the serum
level of testosterone may be considerably higher than the 80
ng/dL maximum considered to be "physiological" and may
functionally be as high as about 400 ng/dL. Hence, in such
situations the effective "physiological range" may vary from
as low as 15 ng/dL up to 400 ng/dL. Depending on the basal
SHBG level of individuals, sometimes the "physiological
20 range" may be from 85 to 300 ng/dL, or 90-250 ng/dL.

In carrying out the present invention, upon determining
the presence of one or more signs and symptoms of
testosterone deficiency in a female receiving oral estrogen

179 182 183

5 therapy (or to be placed on oral estrogen therapy), a
parenteral dose of transdermal patch containing an
androgenic steroid, such as testosterone or other androgen
as previously described, is applied in sufficient quantity
and for sufficient time to reduce symptoms of testosterone
10 deficiency or imbalance of estrogen/androgenic steroid. The
goal is to reduce symptoms of testosterone deficiency or
imbalance of estrogen/androgenic steroid.

In addition to transdermal testosterone patches, other
parenteral systems for delivering androgens include: intra-
5 muscular injections of testosterone esters, subcutaneous
implants of fused testosterone, and topical preparations of
testosterone, methyltestosterone and other androgens.
Devices and methods for those parenteral applications are
well known in the art.

20 As used herein, "application situs" means a site
suitable for topical application by means of an adhesive-
secured, sustained release device, patch, or dressing, e.g.
on the arm, back, chest, abdomen, leg, buttock, etc.
Typically the device will be designed to be worn for 1 to 14

180 113
184

5 days, more usually from 1 to 7 days. The diffusion
coefficient of the androgenic steroid in the carrier vehicle
of the device and the solubilities of the androgenic
steroids in the carrier are important factors. The
transdermal dose of any androgenic steroid may require minor
10 adjustments. However, it is to be noted that the overall
ranges for testosterone are those sufficient to achieve a
testosterone serum level of 15-400 ng/dL. This range may
vary for any given androgenic steroid according to its
relative potency and bioavailability. Therefore the key to
the exact amount is that of functionality. Any androgenic
dosage that produces a serum level equivalent to 15-400
ng/dL of testosterone and results in the desired
physiological effects should be effective. More than one
androgenic steroid or form of testosterone may be combined
20 to achieve the desired result. Testosterone, testosterone
esters, dihydrotestosterone and methyltestosterone, as noted
above, are the preferred androgenic steroid agents for use
herein.

5 In one embodiment, the androgenic steroid is delivered
transdermally via a matrix type patch. The androgen patch
is applied to a subject who is also orally administered
estrogen in an effective quantity. The androgen is
administered in a sufficient quantity to alleviate signs and
10 symptoms attributable to the deficiency or imbalance of
androgenic hormones.

In general, estrogens will be administered orally at a
dosage that is equivalent to about 0.02 to 3.0 mg per day of
conjugated estrogen. The dose will be adjusted according to
an individual woman's needs and the potency of estrogen
administered. The dose of oral estrogens can be taken in a
single daily dose or in two or more smaller quantities.
Generally, for women who are experiencing vasomotor
symptoms, the lowest effective dose of estrogen is used to
control vasomotor instability. Lower doses may be used in
20 women who do not suffer vasomotor symptoms but will benefit
from other health benefits, such as cardiovascular and bone
benefits.

182-115
106

5 Optionally, progestin is also administered to women in
need to protect against endometrial hyperplasia. The
administration of progestin can be done by any method known
in the art according to individual need. Progestins are
also essential active ingredients of many oral contraceptive
10 formulations.

15 . The following examples are illustrative of the results
obtained using coadministration of oral estrogen and
parenteral androgenic steroids to alleviate physiological
symptoms attributable to the deficiency or imbalance of
estrogen and androgenic hormones in females, according to
the invention. It is to be understood that while the
invention has been described in conjunction with the
preferred specific embodiments thereof, that which follows
is intended to illustrate and not limit the scope of the
20 invention. Other aspects of the invention will be apparent
to those skilled in the art to which the invention pertains.

EXAMPLE 1

183-116
407

5 In surgically menopausal women between the ages of 20
and 55 years, oral estrogen and transdermal testosterone are
administered as follows. The estrogen consists of conjugated
equine estrogen (Premarin® tablets) at a daily dose of 0.625
to 2.5 mg. The transdermal testosterone is administered by
10 a matrix type transdermal patch that is applied to the
abdomen twice weekly and has a nominal delivery rate of 300
mcg/day. The duration of coadministration is 12 weeks.
After 12 weeks, this regimen improved sexual function, mood
and well-being in comparison to administration of conjugated
equine estrogen alone.
5

Serum hormone levels measured on this regimen are in
the following ranges: total testosterone (15.5 to 254.3
ng/dL), free testosterone (1.7 to 33.7 pg/mL), estradiol (5
to 280 pg/mL), and estrone (8 to 410 pg/mL). The levels of
20 sex hormone binding globulin range from 62.7 to 563 nmol/L.
It is noteworthy that 73 percent of the women on this
regimen of oral estrogen and transdermal testosterone
achieved total testosterone levels in excess of 80 ng/dL.

184 117 108
5 In contrast, 97 percent had free testosterone levels below
15 pg/mL.

EXAMPLE 2

10 A combination of an androgenic compound and an
estrogenic compound is administered to women who are
naturally menopausal according the following regimen:

15 Androgen: topical administration of testosterone in an
appropriate vehicle, such as a cream or ointment, that may
contain a permeation enhancer such that serum concentrations
20 of free testosterone are in the range of 0.5-15 pg/mL. The
androgen cream may contain cetyl esters, cetyl alcohol,
white wax, glyceryl monostearate, propylene glycol
monostearate, methyl stearate, benzyl alcohol, sodium lauryl
sulfate, glycerin, and mineral oil. The cream may optionally
25 contain a permeation enhancer such that serum concentrations
of total testosterone attained are in the range of 30 - 250
ng/dL. Each gram of the cream contains about 400 mcg
testosterone. About 1 gram of the cream is applied to the
skin or abdomen at bed time.

185 118 189

5 In order to control the amount of testosterone
administered, a meter dosing device can be employed. Dose
adjustments can be made on the basis of either symptom
relief, e.g. restored libido, or to achieve the desired
serum free testosterone serum concentrations. Ranges for
10 symptomatic relief may vary between 1-20 pg/mL.

Estrogenic compound: oral conjugated estrogens tablets
are given at a starting dose of 0.625 mg/day. When
necessary, doses are adjusted upward to 1.25 mg/day for
better control of symptoms, or downward to 0.3 mg/day as
5 vasomotor symptoms subside to maintain bone and serum lipid
benefits.

In women who have an intact uterus, it is important
that a background of a progesterone be present to avoid
endometrial hyperplasia that can result from unopposed
10 estrogen replacement therapy.

Benefits of combined regime of hormones may be
perceptible to the patient within the first 6 weeks of
administration, but variable responses can be expected.

186 119
190

Typically, hormones are administered on a chronic basis to maintain health.

EXAMPLE 3

A combination of an androgenic compound and an estrogenic compound is administered to women who are post-menopausal to alleviate signs and symptoms associated with frailty, such as the loss of bone and muscle mass and function, reduced cognitive abilities and diminished energy.

Androgen: intramuscular injection of 150 mg testosterone enanthate every month. Testosterone enanthate is formulated to contain 200 mg per mL in sesame oil. In order to provide 150 mg of testosterone enanthate, the injected dose is 0.75 mL.

Estrogen: oral estrogens are given in a range of 0.3 to 3.0 mg/day.

Administration is performed as long as benefits of treatment are desired and deemed appropriate by the prescribing physician.

187 720 191

EXAMPLE 4

A combination of an androgenic compound and an estrogenic compound is administered to women with premature ovarian failure, e.g., women whose ovarian function permanently ceases prior to age 40.

Androgen: methyltestosterone is delivered by the buccal route at a dose of 1 mg/day to achieve an improvement in sexual function that is equi-efficacious to that produced by native testosterone at serum levels of about 50 to 300 ng/dL. The buccal tablet is a bilayer tablet consisting of a drug layer and a bio-adhesive layer (both 50 mg each). The composition of the drug layer (in weight percent) is 2% methyltestosterone, 0.75 % magnesium stearate, 0.1% FD&C yellow #6, 24% Klucel HXF, and 73.15% mannitol. The composition of the bio-adhesive layer (in weight percent) is 69.25% polyethylene oxide, 30% carbomer 934P, and 0.75% magnesium stearate. The adhesive side of the tablet is affixed to the gingiva of the upper jaw and the drug side of the tablet faces the overlying buccal mucosa. Drug is

188-101
192

5 absorbed transmucosally as the tablet dissolves over two
hours. The tablet is applied once daily after breakfast.

10 Estrogen: Estrace®, Bristol-Myers Squibb Co., an oral
micronized estradiol product in tablet form, is administered
at a dosage of 2 mg/day to alleviate menopausal symptoms and
prevent bone loss.

In addition a progestin, medroxyprogesterone acetate,
is orally administered at a dose of 5 mg/day for the last
ten days of each month to induce endometrial sloughing.

15 The treatment is administered until the patient reaches
about age 55, at which time it may be modified to other HRT
regimens.

20 These examples are intended to be indicative only of
regimens that can be utilized. Each regimen will preferably
be customized to meet the needs of the patient. While the
examples have been directed primarily to the delivery of an
androgenic steroid to provide needed supplementation based
on determination of a need for such, the administration will
be concurrent with the oral administration of estrogen
formulations.

189 170 193

5 Those skilled in the art will recognize, or be able to
ascertain using no more than routine experimentation, many
equivalents to the specific embodiments of the invention
described herein. Such equivalents are intended to be
encompassed by the following claims.

10
COPYRIGHTED MATERIAL

191 124 195

5 4. A method according to Claim 3 wherein said
androgenic steroid is administered in a dosage sufficient to
maintain a total androgenic steroid serum level equivalent
to a total testosterone serum level of between about 90 and
about 250 ng/dL.

10
15
20 5. A method according to Claim 2 or 3 wherein said
androgenic steroid is a member selected from the group
consisting of native testosterone, testosterone esters,
methyltestosterone, androstenedione, adrenosterone,
dehydroepiandrosterone, fluoxymesterone, methandrostenolone,
17 α -methylnortestosterone, nandrolone and its derivatives,
norethandrolone, dihydrotestosterone, oxymetholone,
stanozolol, ethylestrenol, oxandrolone, bolasterone and
mesterolone.

25
30 6. A method according to Claim 5 wherein said
androgenic steroid is a member selected from the group
consisting of testosterone, testosterone esters,
dihydrotestosterone, and methyltestosterone.

192 125 196

5
7. A method according to Claim 6 wherein the androgenic steroid is a member selected from the group consisting of testosterone and testosterone esters.

10
8. A method according to Claim 7 wherein said androgenic steroid is testosterone.

9. A method according to Claim 6 wherein the androgenic steroid is methyltestosterone.

15
10. A method according to Claim 6 wherein the androgenic steroid is dihydrotestosterone.

20
11. A method according to Claim 2 or 3 wherein said estrogen administered orally is in a dosage range of equivalent to the dose response obtained from administering conjugated estrogen in a dosage range of between 0.02 to 3.0 mg/day.

193 176 497

5 12. A method according to Claim 11 wherein said
estrogen administered orally is selected from a group
consisting of 17β -estradiol, α -estradiol, conjugated
estrogen, esterified estrogens, micronized estradiol, sodium
estrogen sulfate, ethinyl estradiol, estrone, and other
10 estrogenic steroids and derivatives and esters thereof are
representative of estrogens.

13. A method according to Claim 12 wherein said
estrogen administered orally is a conjugated estrogen.

14. A method according to Claim 12 wherein said
estrogen administered orally is a esterified estrogen.

15. A method according to Claim 12 wherein said
estrogen administered orally is a micronized estradiol.

16. A method according to Claim 2 or 3 wherein said
estrogen hormone administered orally is in the form of an
oral contraceptive.

194 127
1990

5 17. A method according to Claim 2 or 3 wherein said
improvement of health is manifest by one or more of the
following parameters: restoration or enhancement of sexual
desire, restoration or enhancement of stimulation to sexual
organs, restored or enhanced ability to achieve orgasm,
10 restoration or enhancement of pleasure in sexual activity,
restoration or enhancement of vital energy and sense of
well-being, enhancement in muscle tone, bone mineral
density, skin and hair, and reduction in vasomotor
instability.

18. A method according to Claim 2 or 3 wherein
progesterone is administered concomitant with estrogen
administration.

19. A method according to Claim 2 or 3 wherein the
parenteral means is selected from the group consisting of
transdermal delivery means, means of topical administration
to the skin, sublingual delivery means, transbuccal delivery

195 128
199

5 means, transmucosal delivery means, intramuscular injection
and subdermal implants.

20. A method according to Claim 19 wherein the
parenteral means is selected from the group consisting of
10 transdermal delivery means, intramuscular injection, and
subdermal implants.

21. A method according to Claim 20 wherein the
parenteral means is intramuscular injection.

22. A method according to Claim 20 wherein the
parenteral means is subdermal implants.

23. A method according to Claim 19 wherein the
parenteral means is a topical cream or gel.

24. A method according to Claim 20 wherein the
parenteral means is a transdermal device.

196 128 200

5 25. A method according to Claim 24 wherein the
transdermal device is a matrix type transdermal device.

26. A method of improving health in a woman receiving
oral estrogen in an oral estrogen regimen, comprising
10 administration of an androgenic steroid by a parenteral
means to achieve a serum level equivalent to a total
testosterone serum level of between 15 and 400 ng/dL.

27. A method according to Claim 26 wherein said woman
15 has an elevated SHBG level and said androgenic steroid is
administered in a dosage sufficient to maintain a total
androgenic steroid serum level equivalent to a total
testosterone serum level of between about 85 and about 300
ng/dL.

28. A method according to Claim 27 wherein said woman
has an elevated SHBG level and said androgenic steroid is
administered in a dosage sufficient to maintain a total
androgenic steroid serum level equivalent to a total

197 130-204

5 testosterone serum level of between about 85 and about 300
ng/dL.

20130405100

198 131 202

5

ABSTRACT OF THE DISCLOSURE

The invention provides methods for coadministration of oral estrogen and parenteral androgenic steroids to alleviate symptoms attributable to the deficiency or imbalance of estrogen and androgenic hormones in females. Optionally, progestins are also administered. Deficiencies are indicated by women having diminished androgen production. The method of improving health in a woman comprises coadministering effective amounts of estrogen and androgenic steroids characterized in that the estrogen is administered orally and the androgenic steroid is administered parenterally. Estrogen administered orally is in a dosage range equivalent to the dose response obtained from administering conjugated estrogens in a dosage range of between 0.02 to 3.0 mg/day. The parenteral administration of androgenic steroid is in a dosage range equivalent to the dosage response obtained from administering testosterone in a dose sufficient to cause a blood level of testosterone, in the women, to be about 15 to 400 ng/dL.

10
15
20

199 132
203

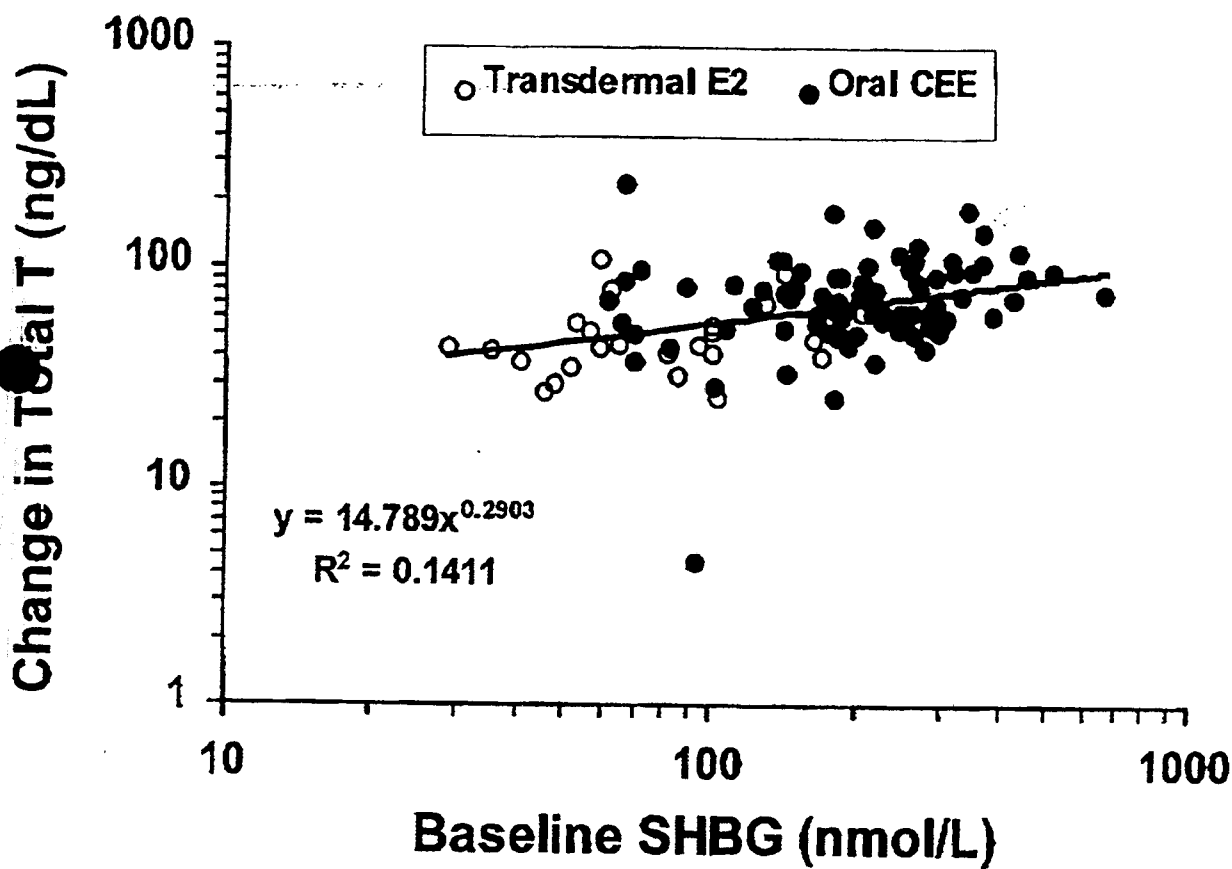


Figure 1

200-777
204

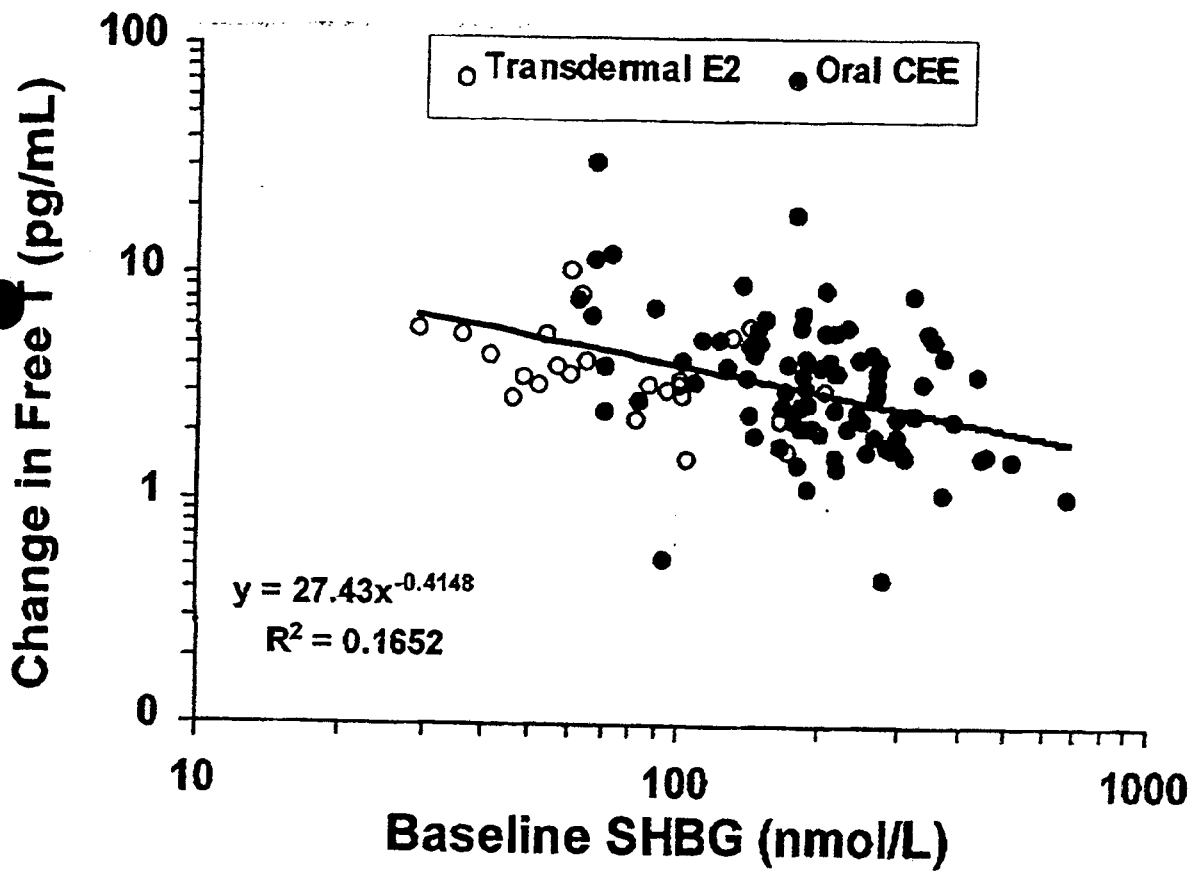


Figure 2

LOS ESTADOS UNIDOS DE AMÉRICA

A TODOS A QUIENES LOS PRESENTES DOCUMENTOS PUDIERAN LLEGAR:

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS

Oficinas de Patentes y Marcas de los Estados Unidos

28 de junio de 2000

POR LA PRESENTE SE CERTIFICA QUE LA ANEXA AQUÍ ES UNA COPIA VERDADERA TOMADA DE LOS REGISTROS DE LA OFICINA DE PATENTES Y MARCAS DE LOS ESTADOS UNIDOS, DE LOS DOCUMENTOS DE LA SOLICITUD DE PATENTE ABAJO IDENTIFICADA QUE SATISFACE LOS REQUERIMIENTOS PARA SERLE OTORGADA UNA FECHA DE PRESENTACIÓN SEGÚN 35 USC 111.

NÚMERO DE SOLICITUD: 60/138,854
FECHA DE SOLICITUD: 11 de junio de 1999

Por la Autoridad del
COMISIONADO DE PATENTES Y MARCAS

(Hay firma ilegible)

T. LAWRENCE
Oficial de Certificaciones

Hay sello seco que dice:
OFICINA DE PATENTES Y MARCAS
ESTADOS UNIDOS DE AMÉRICA

202
12/20

Reivindicaciones

1. Un método para mejorar la salud de una mujer que comprende coadministrar cantidades efectivas de estrógeno y esteroides androgénicos,
5 caracterizado porque el estrógeno se administra oralmente y dichos esteroides androgénicos se administran por medios parenterales.
2. Un método de acuerdo a la reivindicación 1 en donde dicho esteroide androgénico se administra en una dosis suficiente para mantener un
10 nivel de esteroide androgénico total en el suero equivalente a un nivel de testosterona total en el suero de aproximadamente 15 a aproximadamente 400 ng/dL.
3. Un método de acuerdo a la reivindicación 2 en donde dicha mujer tiene un nivel de SHBG elevado y dicho esteroide androgénico se administra
15 en una dosis suficiente para mantener un nivel de esteroide androgénico total en el suero equivalente a un nivel de testosterona total en el suero de entre aproximadamente 85 a aproximadamente 300 ng/dL.
4. Un método de acuerdo a la reivindicación 3 en donde dicho esteroide
20 androgénico se administra en una dosis suficiente para mantener un nivel total de esteroide androgénico en el suero equivalente a un nivel de testosterona total en el suero de entre aproximadamente 90 a aproximadamente 250 ng/dL.
5. Un método de acuerdo a la reivindicación 2 o 3 en donde dicho
25 esteroide androgénico es un miembro seleccionado del grupo consistente de testosterona natural, ésteres de testosterona,

203

137
208

metiltestosterona, androstenediona, adrenosterona, deshidroepiandrosterona, fluoximesterona, metandrostenolona, 17 α -metilnostestosterona, nandrolona y sus derivados, noretandrolona, dihidrotestosterona, oximetolona, estanozolol, etilestrenol, oxandrolona, bolasterona y mesterolona.

- 5 6. Un método de acuerdo a la reivindicación 5 en donde dicho esteroide androgénico es un miembro seleccionado del grupo consistente de testosterona, ésteres de testosterona, dihidrotestosterona y metiltestosterona.
- 10 7. Un método de acuerdo a la reivindicación 6 en donde el esteroide androgénico es un miembro seleccionado del grupo consistente de testosterona, dihidrotestosterona y ésteres de testosterona.
8. Un método de acuerdo a la reivindicación 7 en donde dicho esteroide androgénico es testosterona.
- 15 9. Un método de acuerdo a la reivindicación 6 en donde el esteroide androgénico es metiltestosterona.
10. Un método de acuerdo a la reivindicación 6 en donde el esteroide androgénico es dihidrotestosterona.
11. Un método de acuerdo a la reivindicación 2 ó 3 en donde dicho
- 20 estrógeno administrado oralmente está en un intervalo de dosis equivalente a la respuesta a la dosificación obtenida al administrar estrógeno conjugado en un intervalo de dosis de entre 0.02 a 3.0 mg/día.
12. Un método de acuerdo a la reivindicación 11 en donde dicho
- 25 estrógeno administrado oralmente es seleccionado del grupo consistente de 17 β -estradiol, α -estradiol, estrógeno conjugado,

estrógenos esterificados, estradiol micronizado, estrógeno sulfato de sodio, etinil estradiol, estrona, otros esteroides estrogénicos y derivados y ésteres de los mismos.

13. Un método de acuerdo a la reivindicación 12 en donde dicho estrógeno administrado oralmente es un estrógeno conjugado.
14. Un método de acuerdo a la reivindicación 12 en donde dicho estrógeno administrado oralmente es un estrógeno esterificado.
15. Un método de acuerdo a la reivindicación 12 en donde dicho estrógeno administrado oralmente es un estradiol micronizado.
16. Un método de acuerdo a la reivindicación 2 ó 3 en donde dicha hormona estrógeno administrada oralmente está en la forma de un anticonceptivo oral.
17. Un método de acuerdo a la reivindicación 2 ó 3 en donde dicho mejoramiento de salud fisiológica es manifestado por uno ó más de los siguientes parámetros: restauración ó mejoría del deseo sexual, restauración ó mejoría de la estimulación a los órganos sexuales, restauración o mejoría de la habilidad para alcanzar orgasmos, restauración ó mejoría del placer en la actividad sexual, restauración ó mejoría de la energía vital y sentido de bienestar, mejoría en el tono muscular, en la densidad mineral del hueso, en la piel y el cabello, y reducción en la inestabilidad vasomotora.
18. Un método de acuerdo a la reivindicación 2 ó 3 en donde la progesterona es administrada concomitantemente con la administración de estrógeno.
19. Un método de acuerdo a la reivindicación 2 ó 3 en donde el medio parenteral es seleccionado del grupo consistente de medios de

205
139
210

liberación transdérmica, medios de administración tópica a la piel, medios de liberación sublingual, medios de liberación transbucal, medios de liberación transmucosal, inyección intramuscular e implantes subdérmicos.

- 5 20. Un método de acuerdo a la reivindicación 19 en donde el medio parenteral es seleccionado del grupo consistente de medio de liberación transdérmica, inyección intramuscular, e implante subdérmico.
21. Un método de acuerdo a la reivindicación 20 en donde el medio parenteral es inyección intramuscular.
- 10 22. Un método de acuerdo a la reivindicación 20 en donde el medio parenteral es implante subdérmico.
23. Un método de acuerdo a la reivindicación 20 en donde el medio parenteral es un gel ó crema tópica.
24. Un método de acuerdo a la reivindicación 20 en donde el medio
- 15 parenteral es un dispositivo transdérmico.
25. Un método de acuerdo a la reivindicación 24 en donde la inyección transdérmica es una matriz de tipo dispositivo transdérmico.
26. Un método de mejoramiento de la salud en una mujer que recibe estrógeno oral en un régimen de estrógeno oral, que comprende
- 20 administración de un esteroide androgénico por un medio parenteral para alcanzar un nivel en el suero equivalente a un nivel total de testosterona en el suero de entre 15 y 400 ng/dL.
27. Un método de acuerdo a la reivindicación 26 en donde dicha mujer tiene un nivel elevado de SHBG y dicho esteroide androgénico se
- 25 administra en una dosis suficiente para mantener un nivel total de

206

140
211

esteroide androgénico en el suero equivalente al nivel de testosterona total en el suero de entre 85 y aproximadamente 300 ng/dL.

28. Un método de acuerdo a la reivindicación 27 en donde dicha mujer tiene un nivel elevado de SHBG y dicho esteroide androgénico se
- 5 administra en una dosis suficiente para mantener un nivel de esteroide androgénico total en el suero equivalente a un nivel de testosterona total en el suero de entre 85 y aproximadamente 300 ng/dL.

PA 268646

P. 343

442
212
207

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

June 28, 2000

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: 60/139,323

FILING DATE: June 11, 1999



**By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS**

T. Lawrence

**T. LAWRENCE
Certifying Officer**

PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISION APPLICATION under 37 CFR 1.53 (b)(2).

Docket Number T7118		Type a plus sign (+) inside this box→		+	
INVENTOR(s)/APPLICANT(s)					
LAST NAME	FIRST NAME	MIDDLE INITIAL	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)		
Mazer	Norman	A.	4641 S. Hunters Ridge Circle Salt Lake City, Utah 84124		
TITLE OF THE INVENTION (280 characters max)					
A METHOD OF COADMINISTERING ORAL ESTROGEN AND TRANSDERMAL ANDROGENIC STEROIDS TO WOMEN TO OPTIMIZE PHYSIOLOGICAL RESPONSE					
CORRESPONDENCE ADDRESS					
M. Wayne Western THORPE, NORTH & WESTERN, L.L.P. P.O. BOX 1219 SANDY					
STATE	UTAH	ZIP CODE	84091-1219	COUNTRY	USA
ENCLOSED APPLICATION PARTS (check all that apply)					
☒ Specification (Number of Pages) <u>57</u>		☐ Small Entity Status			
☒ Drawing(s) (Number of Pages) <u>2</u>		☐ Other (specify) 			
METHOD OF PAYMENT (check one)					
☒ A check or money order is enclosed to cover the Provisional filing fees			PROVISIONAL FILING FEE AMOUNT (\$)		\$150.00
☒ The commissioner is hereby authorized to charge filing fees and credit Deposit Account Number: <u>20-0100</u>			Deficiencies Only		

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are: _____

Respectfully submitted,

SIGNATURE M. Wayne Western Date 6/11/99 Express No. EL163093576US

TYPED or PRINTED NAME M. Wayne Western REGISTRATION NO. (if appropriate) 22,788

☒ Additional inventors are being named on separately numbered sheets attached hereto

PROVISIONAL APPLICATION FILING ONLY

Burden Hour Statement: This form is estimated to take 2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Office of Assistance Quality and Enhancement Division, Patent and Trademark Office, Washington, DC 20231 and to the Office of Information and Regulatory Affairs, Office of Management and Budget (Project 0651-00XX), Washington, DC 200503 DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS SENT TO Commissioner of Patents and Trademarks, Washington, DC 20231

06/11/99
JCS62 U.S. PTO

208 213
JCS41 U.S. PTO
60/139323
06/11/99

PROVISIONAL APPLICATION COVER SHEET (CONTINUED)

209
144
214

ADDITIONAL INVENTOR(s)/APPLICANT(s)			
LAST NAME	FIRST NAME	MIDDLE INITIAL	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)
Rosario-Jansen	Theresa		6773 Little River Lane Loveland, OH 45140

210

145
215

5 EXPRESS LABEL NO. 3L163093576US

PATENT APPLICATION

ATTORNEY DOCKET T7118

10

A METHOD OF COADMINISTERING ORAL ESTROGEN AND TRANSDERMAL
ANDROGENIC STEROIDS TO WOMEN TO OPTIMIZE PHYSIOLOGICAL
RESPONSE

15

TECHNICAL FIELD

20

25

This invention relates to a method of alleviating signs
and symptoms attributable to the deficiency or imbalance of
estrogen and androgenic hormones in females. Particularly,
it is directed to methods of administration of parenteral
androgenic steroids to women who are taking estrogen orally,
to maintain free testosterone serum levels within the normal
physiological range. Such level may be necessary to be
functional to alleviate various signs and symptoms
attributable to the deficiency or imbalance of estrogen and
androgenic hormones, thus providing to females an optimal
effect on sexual function, energy and sense of well-being.

THORPE, NORTH & WESTERN, LLP
P. O. Box 1219
Sandy, Utah 8491-1219
Telephone (801) 566-6633

211
146
210

5 BACKGROUND

There are a variety of conditions in which women express hormonal imbalance. Women who are menopausal, either naturally or as a result of ovarian failure or loss (e.g., secondary to hysterectomy, surgical oophorectomy or chemotherapy), frequently develop estrogen and testosterone deficiencies with their attendant undesirable effects. In these women, the need for estrogen replacement therapy (ERT) is determined by symptoms developed by a woman or, in some cases, by a blood test to determine serum estrogen levels.

15 Another situation in which women may express hormonal imbalance is when they are receiving estrogen-containing oral contraceptives. By suppressing ovarian function, oral contraceptives diminish testosterone production resulting in androgen deficiency in these pre-menopausal women.

20 Use of oral estrogens causes an increase in a woman's sex hormone binding globulin (SHBG). SHBG is a protein produced by the liver that tightly binds estrogen and testosterone in the blood. In its bound state, the sex hormone is not available to exert its biological action at

212 147 219

5 receptors in target tissues. Not only is SHBG-bound hormone
not available to bind to receptors, it is also not available
for metabolic clearance. Hence, women receiving oral
estrogen therapy can become functionally testosterone
deficient for two reasons. First, estrogen administration
10 lowers or suppresses the pituitary luteinizing hormone (LH),
which stimulates the ovarian production of testosterone.
Second, by increasing SHBG levels, the availability of
testosterone is diminished or deficient.

In contrast to the effects of oral estrogen
15 administration, SHBG does not increase when estrogens are
provided by non-oral delivery routes, such as transdermal
delivery of estrogens. A comparison of mean SHBG levels in
oophorectomized women receiving either no estrogen
replacement therapy, transdermal estradiol (0.1 mg/day) or
20 oral conjugated equine estrogen (1.25 mg/day) is given in
Table 1.

213 148 218

5

Table 1

Hormone data (mean $\pm$ SEM) in three groups of surgically menopausal women evaluated in pharmacokinetic studies of testosterone matrix patches. Each woman received 300 mcg/day of testosterone delivered transdermally from a matrix patch.

10

Hormone (unit)	No ERT n=19	Transdermal E2 (0.1 mg/day) n=12	Oral CEE (1.25 mg/day) n=13
Baseline SHBG Levels (nmol/L)	85.6 $\pm$ 9.6	90.8 $\pm$ 12.9	226.3 $\pm$ 13.5
Change in total T (ng/dl)	57.2 $\pm$ 4.4	53.6 $\pm$ 7.2	70.8 $\pm$ 9.6
Change in Free T (pg/mL)	4.60 $\pm$ 0.40	4.20 $\pm$ 0.70	2.56 $\pm$ 0.30

15

In the above table:

20

E2 is estradiol

T is testosterone

CEE is conjugated equine estrogens

25

As shown in Table 1, SHBG levels in the oral estrogen group are approximately 2.5-fold larger than the other groups and exceed the upper limits of the normal range. In the transdermal estradiol group, SHBG levels are comparable

214 149
219

5 to the untreated patients. The differential effects of oral and transdermal estrogen on SHBG levels are believed to result from the hepatic first-pass effect of the oral estrogen administration, which either raises hepatic SHBG production or diminishes hepatic clearance of SHBG.

10 As a corollary to the differential effects of oral and transdermal estrogen on SHBG levels, the levels of total and free (unbound) testosterone that are attained with parenteral testosterone administration also differ. As shown in Table 1, in the case of transdermal testosterone
15 administration at the dosage of 300 mcg/day, the changes in total testosterone levels are approximately 30% larger for the oral estrogen group than the other groups. In contrast, the changes in free testosterone levels are approximately 40% lower for the oral estrogen group than the other groups.
20 It is generally recognized that both the free testosterone and the albumin-bound fraction of testosterone are bioavailable to interact at receptors, and the sum of these are termed the "bioavailable testosterone" fraction. Herein, we will use the terminology "free" testosterone to

215

156
220

5 connote the functional level of testosterone since it is the more commonly measured serum component.

The greater increase in total testosterone levels associated with oral estrogen administration is presumably due to the decrease in testosterone clearance that results from the elevation in SHBG levels and the corresponding reduction in the free fraction of testosterone. Conversely, the smaller increase in free testosterone levels with oral estrogen administration indicates that the reduction in the free fraction exceeds the reduction in testosterone clearance.

The latter is a new and unexpected finding that could not have been predicted from earlier studies of testosterone clearance. As a general consequence of these phenomena, one would expect that for a given regimen of parenteral testosterone delivery to women, total testosterone will increase while free testosterone will decrease as a function of increasing SHBG levels. This finding is illustrated with individual patient data compiled from three studies in which women on oral or transdermal estrogen received transdermal

216 151 221
5 testosterone at a nominal delivery rate of 300 mcg/day (see
Figures 1 and 2). As depicted on logarithmic scales,
changes in total T increased significantly, while changes in
free T decreased significantly as a function of SHBG level.

From the perspective of achieving the beneficial
10 effects of parenteral testosterone therapy in testosterone-
deficient women concomitantly receiving oral estrogen, these
data have three key implications:

First, the total testosterone levels attained during
treatment may substantially exceed the upper limit of the
15 normal physiological range of testosterone levels, as
determined in women with normal SHBG levels. Second, since
free testosterone levels are believed to exert the
biological effects of testosterone on target tissues, they
are preferable to the total testosterone in monitoring
20 therapy, and should not substantially exceed the upper limit
of the normal range in most circumstances. Third, for women
with inordinate elevations in SHBG, the total parenteral
delivery rate of testosterone necessary to achieve
beneficial and safe effects may exceed the previously

217 150 222

5 defined ranges such as described by Ebert, et al. in U.S.
Patent 5,460,820. This range was reported to be 50-500
mcg/day for testosterone from a transdermal patch dosage
form, with or without the concomitant administration of
estradiol from the same patch. The present invention is
10 mainly directed to delivery rates of testosterone necessary
to maintain the free testosterone with a range of about 0.1
and about 15 pg/mL. Two copending applications, filed under
Thorpe, North & Western docket numbers T7797 and T7798 on
even date herewith, are directed to total testosterone
15 levels and free testosterone levels associated with SHBG
elevation attendant with orally administered estrogens.

In women who have a uterus, it is imperative that they
receive a concomitant progesterone, as unopposed estrogen
use is associated with endometrial hyperplasia which can
20 lead to uterine cancer. Progesterone and synthetic analogs
thereof may prevent this unwanted estrogen effect.
Progestins are also utilized in oral contraceptives.

The oral administration of estrogen to females,
particularly such as in postmenopausal or oophorectomized

218 157 223

5 women (i.e. women who have had one or both of their ovaries
removed), is common. In the context of estrogen replacement
therapy, researchers and medical practitioners have long
recognized the need to administer estrogen to make up for or
supplement the production of estrogen in women who have need
10 thereof. Conjugated estrogens, in dosage ranges of about
0.02 to 3.0 mg/day (or the equivalent of other estrogens,
such as micronized estradiol or ethinyl estradiol, to obtain
the same response) are orally administered to supplement
decreasing or lack of ovarian function. Synthetic
15 progestin, such as norethindrone acetate, can be
administered orally or transdermally to prevent endometrial
hyperplasia. To control conception in the case of oral
contraceptives, ethinyl estradiol is administered in a
regimen known in the art, typically in a range of about 0.02
20 to about 0.035 mg/day.

However, it is recognized that merely supplementing
estrogen is not sufficient to maintain the health and well
being of the female body. Many women continue to experience

219 154 224

5 symptoms such as loss of sexual desire, diminished vital energy, a sense of well-being, and loss of muscle tone.

10 In the female, androgens are produced by the adrenal glands and ovaries in small amounts and have multiple effects on a variety of target tissues, e.g., muscle, bone, skin, brain, and genitalia. Recent research has shown that androgens, and particularly testosterone, contribute substantially to bone density, as well as to muscle tone and certain cognitive abilities. Several reports in the literature establish the beneficial effects of androgen therapy on sexual function.

15 Ebert, et al., U.S. Patent 5,460,820, in one aspect, teaches a composition and method for coadministering estrogen and testosterone transdermally via a patch delivery system. However, in many instances it may be more advisable to administer estrogen orally to a woman who has a need for estrogen replacement therapy (ERT), such as postmenopausal or oophorectomized women, as referenced above. Further, it may be advantageous to administer androgens by other parenteral routes, depending on the individual patient's

220 155
225

5 characteristics and preferences. It is recognized that
parenteral delivery of androgens is safer to the liver and
provides more sustained delivery than oral routes since the
first pass metabolism effects are bypassed. On the other
hand, oral delivery of estrogens allows for an improved
10 serum lipid profile.

Ebert, et al., supra, is drawn to a method for
maintaining total testosterone serum blood levels in a
"physiological range" of between about 15 to 80 ng/dL by
means of transdermally administering about 50 to 500 mcg/day
15 of testosterone from a testosterone matrix transdermal
delivery system. Other publications indicate the
physiological total testosterone serum range may vary
somewhat, but is generally within the above stated
parameters. However, it has been discovered that the above-
20 stated total testosterone serum levels for females may not
be an accurate indicator of functional testosterone levels
in women receiving oral estrogen therapy. Oral estrogens
tend to decrease or suppress androgenic steroid secretion
and increase the production of sex-hormone binding globulin

221 156
226

5 (SHBG). Also, as discussed above, SHBG binds testosterone,
thereby decreasing its bioavailability to target tissues.
Therefore, in order for the female receiving oral estrogen
to have adequate testosterone to obtain a desired
physiological response, it may be necessary that the
10 delivery rate of testosterone be sufficient to achieve and
maintain free testosterone level within a range of 0.5-15
pg/ml, namely, with a delivery rate of 50-1000 mcg/day.

In view of the above, it would be desirable to provide
compositions and methods for their administration that would
15 enable women exhibiting symptoms attributable to the
deficiency or imbalance of estrogen and androgenic hormones
to take supplemental amounts of oral estrogen and parenteral
androgenic steroids in such a manner as to maintain a
balanced, functional serum level of estrogen and androgenic
20 hormones. It would be further desirable to administer
supplemental amounts of parenteral androgenic steroids in
women receiving estrogen-containing contraceptives. Such
functional level of androgenic hormones in females promotes
the return of sexual health and activity, feelings of well-

222 157
222

5 being, cardiovascular and coronary health, decreases breast
tenderness, maximizes muscle tone and inhibits bone loss,
decreases vasomotor instability, and may enhance certain
cognitive abilities. The present invention is drawn to
attaining these goals by administration of parenteral
10 androgenic steroids to women in need thereof receiving oral
estrogen.

SUMMARY OF THE INVENTION

One object of the present invention is to provide a
15 method of improving health in a woman comprising
coadministering effective amounts of estrogen and androgenic
steroids characterized in that the estrogen is administered
orally and the androgenic steroid is administered
parenterally. In a related aspect, an object of the
20 invention is to provide a method of improving health in a
woman receiving estrogen orally in accordance with a regimen
(e.g., ERT or oral contraceptive), the method comprising
administering to the woman an androgen steroid parenterally.
Estrogen, based on conjugated estrogen, is typically

223 158
220

5 administered orally in a dosage range of between about 0.3
to 3.0 mg/day in women receiving ERT. In an oral
contraceptive context, estrogen is typically administered in
the form of ethinyl estradiol in a dosage range of between
about 0.02 to 0.035 mg/day. The androgenic steroid is
10 parenterally administered at a delivery rate that is
sufficient to achieve and maintain free testosterone (FT)
serum levels in the woman, based on native testosterone, in
a range of between about 0.5 and about 15 pg/mL, namely,
with a delivery rate of 50-1000 mcg/day. As will be
15 discussed below, because of the surprising effect of SHBG in
women receiving oral estrogen, the levels of delivered
testosterone and total serum testosterone required to obtain
the desired FT levels is higher than previously expected.
Dosage forms of other estrogens, for example micronized
20 estradiol, and other androgens, for example, methyl
testosterone, are formulated to yield an equivalent response
to conjugated estrogen and testosterone.

Another object of the present invention is to improve
health in a woman comprising coadministering effective

228 159 229

5 amounts of oral estrogen and parenteral androgenic steroids,
wherein the improvement of health is manifest by one or more
of the following parameters: restoration or enhancement of
sexual desire, restoration or enhancement of stimulation to
sexual organs, restored or enhanced ability to achieve
10 orgasm, restoration or enhancement in pleasure in sexual
activity, restoration or enhancement of vital energy and
sense of well-being, improvement or enhancement in muscle
tone, skin and hair appearance, restoration or improvement
in cognition, increased bone mineral density, improvement in
15 blood lipids, improvement in cardiovascular tone and
responsivity, and reduction in vasomotor instability.

These and other objects are accomplished by providing a
method of improving health in a woman comprising
coadministering effective amounts of estrogen and androgenic
20 steroids characterized in that said estrogen is administered
orally and said androgenic steroid is administered
parenterally.

Estrogen, based on conjugated estrogen, is administered
orally in a dosage range of between about 0.02 to 3.0

225 160
230

5 mg/day, the specific dosage being dependent on the nature of
the estrogen background (e.g., ERT or oral contraceptive),
as well as individual patient needs. The androgenic steroid
is parenterally administered at a delivery rate that is
sufficient to achieve and maintain free testosterone (FT)
10 serum levels of about 0.5-15 pg/mL and preferably 1-15
pg/mL, namely, with a delivery rate of 50-1000 mcg/day.
Dosage forms of other estrogens and androgens are formulated
to yield an equivalent response to conjugated estrogen and
testosterone.

15 Any functional androgenic steroid may be administered.
Representative androgenic steroids are members selected from
the group consisting of native testosterone, testosterone
esters, methyltestosterone and other 17-alkylated versions,
androstenedione, adrenosterone, dehydroepiandrosterone,
20 fluoxymesterone, methandrostenolone, 17 α -
methylnortestosterone, norethandrolone, dihydrotestosterone,
oxymetholone, nandrolone and its derivatives, stanozolol,
ethylestrenol, oxandrolone, bolasterone and mesterolone.
Preferably, the androgenic steroid is a member selected from

226
161
231

5 the group consisting of testosterone, testosterone esters,
dihydrotestosterone and methyltestosterone. Most preferably,
the androgenic steroid is selected from the group consisting
of testosterone, dihydrotestosterone, or testosterone esters
such as testosterone cypionate, testosterone enanthate,
10 testosterone phenylacetate, and testosterone propionate.

The preferred means for parenterally administering the
androgenic steroid is transdermal delivery. For transdermal
delivery, preferred are the matrix or container type of
patches. Matrix type patches are most preferred.

15

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows change in total testosterone level versus
baseline SHBG level during application of transdermal
testosterone patch (300 mcg/day nominal delivery) to
20 patients concomitantly receiving transdermal estradiol or
oral conjugated equine estrogens. Equation describes power
law fit to data with corresponding R-square value.

FIG. 2 shows the change in free testosterone level
versus baseline SHBG level during application of transdermal

227 167 232

5 testosterone patch (300 mcg/day nominal delivery) to patients concomitantly receiving transdermal estradiol or oral conjugated equine estrogens. Equation describes power law fit to data with corresponding R-square value.

10 DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to methods for coadministering oral estrogen and parenteral androgenic steroids, in effective amounts, to women who are in need of supplementation, such as women exhibiting symptoms

15 attributable to the deficiency or imbalance of estrogen and androgenic hormones due to menopause and/or natural aging or as a result of hysterectomy, oophorectomy or ovarian failure (e.g., consequent to chemotherapy), or adrenal insufficiency.

20 The invention relates to a method of coadministration of oral estrogen and parenteral androgenic steroids to women in need to alleviate symptoms attributable to the deficiency or imbalance of estrogen and androgenic hormones and to provide optimal effects on health, sexual function and well-

228 163
230

5 being. With respect to androgenic hormones, the method will
comprise administering androgen in a dose equivalent to
delivering testosterone at a rate from about 50 to 1000
mcg/day, preferably from about 300-1000 mcg/day, more
preferably 500-1000 mcg/day, and most preferably from about
10 550 mcg/day to about 800 mcg/day. As indicated, the
testosterone delivering rate, as well as the total serum
testosterone levels, required to achieve these levels may be
higher than previously expected, due to the elevated SHBG
levels in women receiving oral estrogen.

15 Before the present methods of improving health in a
woman are disclosed and described, it is to be understood
that this invention is not limited to the particular process
steps and materials disclosed herein as such process steps
and materials may vary somewhat. It is also to be
20 understood that the terminology employed herein is used for
the purpose of describing particular embodiments only and is
not intended to be limiting since the scope of the present
invention will be limited only by the appended claims and
equivalents thereof.

229 164 234

5 In describing and claiming the present invention, the following terminology will be used in accordance with the definition set out below.

As used within the context of this invention, the term "coadministration" means administration of multiple active substances to one individual, either simultaneously or sequentially. Thus, the term includes any situation in which women are receiving oral estrogen and parenteral androgen. The term does not imply that the estrogen and androgen actives have to be administered at the same time. Rather, as long as a woman is receiving estrogen orally, administration of parenteral androgen to maintain the desired free testosterone levels will be within the present definition for "coadministration". For example, parenteral administration of androgenic steroids to an individual who has previously been placed on oral estrogen therapy is within the meaning of "coadministration" in the present application. Thus, it is clear that the estrogen and the androgen actives need not be provided in a single product to be "coadministered".

230
165
235

5 As used within the context of this invention, the terms
"androgenic steroid", "testosterone agent" or "testosterone"
(when used generically), must be taken in context and are
generally meant to encompass any androgenic steroid that is
functional in reducing signs and symptoms of testosterone
10 deficiency in females. Members selected from the group
consisting of native testosterone, testosterone esters,
methyltestosterone and other 17-alkylated versions, methyl
testosterone esters, androstenedione, adrenosterone,
dehydroepiandrosterone, fluoxymesterone, methandrostenolone,
15 17 α -methylnortestosterone, norethandrolone,
dihydrotestosterone, oxymetholone, nandrolone and its
derivatives, stanozolol, ethylestrenol, oxandrolone,
bolasterone and mesterolone are representative of androgenic
steroids. Of this group testosterone, dihydrotestosterone,
20 testosterone esters and methyltestosterone are preferred.
Representative esters include the propionate, phenylacetate,
enanthate and cypionate esters of testosterone.

 The term "parenteral" refers to any route of
administration other than the gastrointestinal tract and

231
166
2256

5 includes, but is not limited to: intramuscular injections;
subcutaneous injections or implants; transdermal, e.g.,
patch, lotion, cream, gels, sprays; transmucosal, e.g.,
buccal, sublingual, vaginal and rectal.

10 The terms "estrogen", "estrin" or "estrogenic hormone"
(when used generically) refers to any substance, natural or
synthetic, that exerts biological effects characteristic of
estrogenic hormones such as estradiol and equivalents
thereof. Members selected from the group consisting of 17β -
estradiol, α -estradiol, conjugated estrogens, esterified
15 estrogens, micronized estradiol, sodium estrogen sulfate,
ethinyl estradiol, estrone, and other estrogenic steroids
and derivatives and esters thereof are representative of
estrogens. Representative esters include estradiol-3,17-
diacetate, estradiol-3-acetate, estradiol-17-acetate,
20 estradiol-3,17-divalerate, estradiol-3-valerate, estradiol-
17-valerate. Of this group 17β -estradiol, and corresponding
pivalate, propionate, cypionate, benzoate, and like esters
are preferred.

232
161
237

5 As used herein the term "endogenous free testosterone
level" or "physiological free testosterone level" shall
refer to the free testosterone (FT) serum level that is
normally found in adult women without symptoms associated
with testosterone deficiency and/or imbalanced
10 estrogen/androgen symptoms. For purposes of this invention
this level is between 0.5 and 15 pg/mL. This level is
independent of the observed or generally accepted
physiological total testosterone serum levels.

15 The term "oral estrogens" refers to any estrogenic
hormone which is in a dosage form suitable for oral
administration. Conjugated estrogens, esterified estrogens
and micronized estradiol are the most preferred in an ERT
context. Commercially available oral products of estrogens
include conjugated estrogens available under the trade name
20 Premarin® from Wyeth-Ayerst Laboratories, and esterified
estrogens available under the trade name Estratab® from
Solvay Pharmaceuticals. Ethinyl estradiol is the most
preferred estrogen in oral contraceptives.

233 168 258

5 The term "progesterone" refers to native progesterone, medroxyprogesteroneacetate, norethindrone, and norethindrone acetate and the equivalents thereof.

 As used herein the terms "serum level", "blood level", "total blood level", and "endogenous serum level" include
10 the serum levels of total testosterone or estradiol, including protein-bound and free form of serum testosterone. According to published standards, the total testosterone range in normal, healthy women who are not receiving drugs that alter SHBG is about 15-80 ng/dL; whereas for estradiol
15 it is about 25-200 pg/mL. In the case of the derivatives of testosterone or estradiol, amounts that provide equivalent androgenic or estrogenic activity, as the case may be, to the natural hormones are intended.

 The term "serum total testosterone" refers to the value
20 obtained when testosterone is measured by an appropriate radioimmunoassay (RIA). It is generally accepted that the total testosterone fraction consists mainly of three components: (1) unbound, or free testosterone; (2) albumin-bound testosterone; and (3) SHBG-bound testosterone. Either

2341 160
239

5 free or bioavailable testosterone, i.e. the concentration of
non-SHBG bound testosterone, can be indicative of the
functional level of testosterone in the blood. Total serum
testosterone can be measured by RIA at a clinical
laboratory, using standard techniques, for example, the RIA
10 procedure used by Endocrine Sciences, Inc. (Calabasas Hill,
CA). According to such procedure, serum samples are
extracted with hexane:ethyl acetate. The extract is then
applied to Al2O3 micro columns. The columns are washed with
hexane containing 0.55% ethanol. Finally, testosterone is
15 specifically eluted using hexane containing 1.4% ethanol.
Duplicate aliquots are then taken for RIA. Purified samples
are incubated with an antibody made to a testosterone-3-
oxime-BSA conjugate. Free and antibody-bound testosterone
in each sample is calculated from a curve generated by
20 purified testosterone standards. Sensitivity of the method
is 3 ng/dL when a normal 0.5 ml serum aliquot is used.

The term "serum bioavailable testosterone" refers to
the fraction of testosterone in the serum that is not bound
by SHBG, and can be measured by standard commercial

235 170 240

5 laboratories, for example, the following procedure at
Endocrine Sciences, Inc. Sample preparation begins with an
ammonium sulfate precipitation of the SHBG-bound
testosterone in the serum sample. Then, the amount of
testosterone remaining in the sample is determined using the
10 total testosterone remaining in the sample, using the total
testosterone determination.

The term "serum free testosterone" refers to the
fraction of testosterone in the serum that is not protein
bound and is measured according to the following procedure
15 at, for example, Endocrine Sciences, Inc. Serum is placed
inside a semipermeable dialysis bag and dialyzed against a
buffer containing tritium labeled testosterone outside the
dialysis bag. The percent free testosterone is calculated
from the ratio of radioactivity outside the bag versus
20 inside the bag. This percent free testosterone, multiplied
by the total testosterone in the serum and corrected for
units, results in the concentration of free testosterone in
the serum. Protein levels are checked in the dialysate to

236 T 241
5 be sure the dialysis bag has not leaked. The minimum reportable free fraction is 0.1 percent free.

As used herein, "SHBG" is the protein sex hormone binding globulin in the serum that can be measured by a commercial laboratory standard method, e.g., the
10 immunoradiometric assay from Endocrine Sciences, Inc. A monoclonal antibody made to human SHBG is coated onto plastic beads. The sample and a different SHBG monoclonal antibody, which is labeled with ^{125}I , are incubated overnight with the antibody coated bead. SHBG in the sample and the
15 standard form BEAD-ANTIBODY-SHBG-ANTIBODY ^{125}I sandwiched complexes, attaching ^{125}I label to the beads. The beads are then washed to removed unbound label, and are counted.

As used herein, "transdermal" or "percutaneous" delivery means delivery of an androgenic steroid by passage
20 into and through the skin tissue. Terms "skin," "derma," "epidermis," and the like shall be used interchangeably unless specifically stated otherwise.

The term "diffusional communication" intends that when a transdermal androgenic steroid device of the invention is

238 173 249

5 Several parenteral modes of delivery may be employed
for the androgenic compound. These include: transdermal
delivery via patch, gel, cream, ointment, film, or other
means of application to the skin; transmucosal routes, such
as sublingual or buccal routes, which afford more long
10 lasting blood levels than oral delivery; intramuscular
injection; and subdermal implants. The preferred means for
parenteral administrations are by the transdermal route,
intramuscular injection, or subdermal implant. The most
preferred means for transdermally administering the
15 androgenic steroids are the matrix or container type of
patches. Of these systems, the matrix type patches are most
preferred.

For transdermal administration, skin permeation
enhancer(s) may be included in the formulations to enhance
20 the level of skin flux of the hormone. Examples, without
limitation, of skin permeation enhancers that may be used
in, e.g., matrix patches, are those described or referred to
in U.S. Patent Nos 5,122,383 and 5,153,997, the disclosures
of which as they relate to skin permeation enhancers are

239 174 244
5 incorporated by reference. The enhancer will usually
constitute 1 to 20 wt % of the adhesive carrier forming the
matrix.

Patches for transdermal delivery of androgen steroids
may be manufactured by conventional techniques used in the
10 art of transdermal drug delivery devices. For instance, the
hormones, carrier, and enhancers may be mixed in the desired
proportions to form a homogeneous mixture and then cast or
otherwise applied to a backing layer by lamination to a
release liner layer.

15 Obviously, the need for supplementing estrogen and
androgenic steroids should be determined by a physician or
other health care professional based on monitoring signs and
symptoms of estrogen and testosterone deficiency. Not every
female will exhibit the same symptoms and it is possible
20 that testosterone levels might even be within physiological
ranges but, based on other factors, for example, increased
SHBG, testosterone deficiency may still be diagnosed. Such
symptoms might include, but not be limited to, global loss
of sexual desire, decreased sensitivity to sexual

2410 175 245

5 stimulation in the nipples and in the clitoris, decreased
arousability and capacity for orgasm, diminished vital
energy and sense of well-being, and, loss of muscle tone.
Some women also notice other symptoms such as thinning and
loss of pubic hair, genital atrophy not responsive to
10 estrogen, dry and brittle scalp hair, and, dry skin. Other
symptoms, while less documented, include increased risk for
cardiovascular and coronary heart disease, decreased
cognitive abilities and dry eyes in patients suffering from
Sjogren's syndrome. Women who are receiving oral estrogens
15 can also benefit from androgen therapy since it may reduce
the breast tenderness that can occur with estrogen usage.
Owing to the known breast tissue antiproliferative effects,
androgens may also reduce the excess risk of breast cancer
associated with estrogen use.

20 It is therefore highly desirable, if not imperative,
that testosterone supplementation for a female patient be
based on a diagnosis by a physician who prescribes the mode
of application, dosage and duration of treatment.

2411 176 246

5 As described above, one aspect of the present invention is to provide a method of improving health in a woman comprising coadministering effective amounts of estrogen and androgenic steroids characterized in that the estrogen is administered orally and the androgenic steroid is

10 administered parenterally. Estrogen, based on conjugated estrogen, is administered orally in a dosage range of between about 0.02 to 3.0 mg/day. For some women, particularly those women who are not in need of control of vasomotor symptoms, the frequency of dosing may be less

15 often than once per day, which may still maintain benefits for bone health. In the case of oral contraceptive use, ethinyl estradiol is typically given cyclically in a 21 day on, 7 day placebo regimen.

20 The oral administration of estrogens increases the levels of SHBG, which in turn decreases the bioavailable or free testosterone level. Since additionally, SHBG-bound androgen is not as readily available to metabolizing enzymes, metabolic clearance rates are decreased. However, the net effect, which was discovered experimentally, is that

242 117
247

5 the oral estrogens effectively decrease the levels of
circulating functional testosterone(i.e. free or
bioavailable testosterone levels) in a woman's body via an
increase in the SHBG, since the steady state levels of free
or bioavailable testosterone are affected more strongly by
10 the binding to SHBG rather than reduced metabolic clearance
rates. This has not been previously appreciated and is the
basis for achieving supra-physiological levels of total
testosterone in some women receiving oral estrogens.

The administration of androgenic steroid is in a
15 delivery rate range equivalent to the dose response obtained
from administering testosterone in a dosage range resulting
a serum level of about 0.5-15 pg/mL of free
testosterone(FT),namely, a delivery rate of about 50-1000
mcg/day, the exact value varying from patient to patient,
20 and depending on the methodology used. The range 0.5-15
pg/mL free testosterone(FT) corresponds to laboratory values
obtained using a routine clinic measuring technique.

Synthetic androgens serum level may be measured using
gas chromatography combined with mass spectrometry. Those

243 778 245

5 skilled in the art will be able to utilize such analytical methods to determine the serum levels of these synthetic androgens.

Serum free testosterone (FT), as determined by analysis of blood or other body fluid, will generally refer to native testosterone. Based on the above dosages and laboratory tests, one skilled in the art can readily determine what amount of a particular androgenic steroid or testosterone derivative to administer to achieve the desired serum FT levels. What is important is that the dose of the androgenic steroid or testosterone derivative must be sufficient to overcome, or at least alleviate, the deficiency being monitored or treated, without administering too great a dosage. However, it is an object of this invention to provide a method of treating testosterone deficiencies in women who are taking oral dosages of estrogen to alleviate physiological symptoms attributable to the deficiency or imbalance of estrogen and androgenic hormones and to provide optimal effects on health, sexual function, and well-being. Further, since the oral estrogen

244 779 249-
5 increases the amount of SHBG, this invention relates to a
method for overcoming this effect. Due to the natural
variation in hormone sensitivity, the exact dosage is not as
critical as is the obtaining of the resultant physiological
response for that particular patient, which can correspond
10 to a free testosterone serum level of about 0.5-15 pg/mL
free testosterone. What is more important, due to the high
SHBG environment, is that this level corresponds to an
effective level of biologically active testosterone
component.

15 Too high a dosage of testosterone or other androgen
steroids, or application of a dosage for too long a period
of time may be manifest by symptoms of testosterone excess,
i.e., irritability, clitoral enlargement, increased facial
hair and lowering of the voice. The incidence of side
20 effects depends somewhat on the woman's own sensitivity to
androgens, but is also dependent on the level of
bioavailable or free testosterone at the target tissue.
Owing to the potential for side effects, the lowest
concentration that can bring about the desired effects is

245 180 250

5 preferred. Generally speaking, the guidelines contained in the present invention should yield a satisfactory safety profile.

While the invention encompasses the utilization of testosterone, testosterone esters and methyltestosterone, it may be beneficial to utilize methyltestosterone or similarly non-aromatizable androgens, such as dihydrotestosterone, when it is preferred that estradiol levels be maintained at a low level. Methyltestosterone does not tend to aromatize in situ into estradiol, whereas small amounts of testosterone may be converted to estradiol. Use of methyltestosterone is of particular value, for example, in women who develop testosterone deficiency as a result of ovarian failure following chemotherapy for breast cancer and who need to keep their estrogen levels as low as possible. However, while the following examples primarily illustrate the use of testosterone, testosterone esters and methyltestosterone, such are not intended to be a limitation on the invention, as other androgenic steroids may also be

246 18/25

5 utilized to bring about the desired results but may need to
be monitored more carefully.

In the embodiments exemplified in the following
examples, a dosage of about 50-1000 mcg/day, which is
usually sufficient to provide a serum level of about 0.5-
10 15 pg/mL of free testosterone, is administered to a woman
receiving oral estrogen in an ERT regimen or as an oral
contraceptive. In other words, the androgenic steroid is
administered in a dosage range equivalent to the dosage
response obtained from administering sufficient native
15 testosterone or a testosterone ester to produce a serum
level of about 0.5-15 pg/mL of free testosterone and obtain
the desired response in the woman to whom it is
administered. The concentration most appropriate for a
particular woman can be determined empirically (e.g., by
20 varying the delivery dosage and assessing the resulting
effects on sexual sensitivity and general sense of well
being), usually within a serum level of about 0.5-15 pg/mL
of free testosterone. Again, the levels of administration

247 182 252
5 may be higher than previously thought, due to the higher
SHBG levels attendant with oral estrogen delivery.

In carrying out the present invention, upon determining
the presence of one or more signs and symptoms of
testosterone deficiency in a female receiving oral estrogen
10 therapy (or to be placed on oral estrogen therapy),
parenteral dose of transdermal patch containing an
androgenic steroid, such as testosterone or other androgen
as previously described, is applied in sufficient quantity
and for sufficient time to reduce symptoms of testosterone
15 deficiency or imbalance of estrogen/androgenic steroid. The
goal is to reduce symptoms of testosterone deficiency or
imbalance of estrogen/androgenic steroid.

In addition to transdermal testosterone patches, other
parenteral systems for delivering androgens include: intra-
20 muscular injections of testosterone esters, subcutaneous
implants of fused testosterone, and topical preparations of
testosterone, methyltestosterone and other androgens.
Devices and methods for those parenteral applications are
well known in the art.

24/8 143
253

5 As used herein, "application situs" means a site
suitable for topical application by means of an adhesive-
secured, sustained release device, patch, or dressing, e.g.
on the arm, back, chest, abdomen, leg, buttock, etc.
Typically the device will be designed to be worn for 1 to 14
10 days, more usually from 1 to 7 days. The diffusion
coefficient of the androgenic steroid in the carrier vehicle
of the device and the solubilities of the androgenic
steroids in the carrier are important factors. The
transdermal dose of any androgenic steroid may require minor
15 adjustments. However, it is to be noted that the overall
ranges for testosterone are those sufficient to achieve and
maintain overall ranges of androgenic steroid equivalent of
0.5-15 pg/mL free testosterone level, namely a delivery rate
in the range of from about 50 to 1000 mcg/day. This range
20 may vary for any given androgenic steroid according to its
relative potency and bioavailability. Therefore the key to
the exact amount is that of functionality. Any androgenic
dosage that produces a serum level equivalent 0.5-15 pg/mL
of free testosterone should be effective. More than one

249 186
25A

5 androgenic steroid or form of testosterone may be combined to achieve the desired result. Testosterone, testosterone esters, dihydrotestosterone, and methyltestosterone, as noted above, are the preferred androgenic steroid agents for use herein.

10 In one embodiment, the androgenic steroid is delivered transdermally via a matrix type patch. The androgen patch is applied to a subject who is also orally administered estrogen in an effective quantity. The androgen is administered in a sufficient quantity to alleviate signs and
15 symptoms attributable to the deficiency or imbalance of androgenic hormones.

In general, estrogens will be administered orally at a dosage that is equivalent to about 0.02 to 3.0 mg per day of conjugated estrogen. The dose will be adjusted according to
20 an individual woman's needs and the potency of estrogen administered. The dose of oral estrogens can be taken in a single daily dose or in two or more smaller quantities. Generally, for women who are experiencing vasomotor symptoms, the lowest effective dose of estrogen is used to

250 183 255

5 control for vasomotor instability. Lower doses may be used
in women who do not suffer vasomotor symptoms but will
benefit from other health benefits, such as cardiovascular
and bone benefits.

10 Optionally, progestin is also administered to women in
need to protect against endometrial hyperplasia. The
administration of progestin can be done by any method known
in the art according to individual need. Progestins are
also essential active ingredients of many oral contraceptive
formulations.

15 The following examples are illustrative of the results
obtained using coadministration of oral estrogen and
parenteral androgenic steroids to alleviate physiological
symptoms attributable to the deficiency or imbalance of
estrogen and androgenic hormones in females, according to
20 the invention. It is to be understood that while the
invention has been described in conjunction with the
preferred specific embodiments thereof, that which follows
is intended to illustrate and not limit the scope of the

251 786 756

5 invention. Other aspects of the invention will be apparent
to those skilled in the art to which the invention pertains.

EXAMPLE 1

10 In surgically menopausal women between the ages of 20
and 55 years, oral estrogen and transdermal testosterone are
administered as follows. The estrogen consisted of
conjugated equine estrogen (Premarin® tablets) at a daily
dose of 0.625 to 2.5 mg. The transdermal testosterone is
administered by a matrix type transdermal patch that is
15 applied to the abdomen twice weekly and has a nominal
delivery rate of 300 mcg/day. The duration of
coadministration is 12 weeks. After 12 weeks, this regimen
improved sexual function, mood and well-being in comparison
to administration of conjugated equine estrogen alone.

20 Serum hormone levels measured on this regimen are in
the following ranges: total testosterone (15.5 to 254.3
ng/dL), free testosterone (1.7 to 33.7 pg/mL), estradiol (5
to 280 pg/mL), and estrone (8 to 410 pg/mL). The levels of
sex hormone binding globulin ranged from 62.7 to 563 nmol/L.

252 487 257

5 It is noteworthy that 73 percent of the women on this regimen of oral estrogen and transdermal testosterone achieve total testosterone levels in excess of 80 ng/dL. In contrast, 97 percent have free testosterone levels below 15 pg/mL.

10

EXAMPLE 2

A combination of an androgenic compound and an estrogenic compound is administered to women who are naturally menopausal according the following regimen:

15 Androgen: topical administration of testosterone in an appropriate vehicle, such as a cream or ointment, that may contain a permeation enhancer such that serum concentrations of free testosterone are in the range of 0.5-15 pg/mL. The androgen cream may contain cetyl esters, cetyl alcohol, 20 white wax, glyceryl monosterate, propylene glycol monosterate, methyl stearate, benzyl alcohol, sodium lauryl sulfate, glycerin, and mineral oil. The cream may optionally contain a permeation enhancer such that serum concentrations of total testosterone attained are in the range of 30 - 250

253 148 258

5 ng/dL. Each gram of the cream contains about 400 mcg
testosterone. About 1 gram of the cream is applied to the
skin or abdomen at bedtime.

10 In order to control the amount of testosterone
administered, a meter dosing device can be employed. Dose
adjustments can be made on the basis of either symptom
relief, e.g. restored libido, or to achieve the desired
serum free testosterone serum concentrations. Ranges for
symptomatic relief may vary between 1-20 pg/mL.

15 Estrogenic compound: oral conjugated estrogens tablets
are given at a starting dose of 0.625 mg/day. When
necessary, doses are adjusted upward to 1.25 mg/day for
better control of symptoms, or downward to 0.3 mg/day as
vasomotor symptoms subside to maintain bone and serum lipid
benefits.

20 In women who have an intact uterus, it is important
that a background of a progesterone be present to avoid
endometrial hyperplasia that can result from unopposed
estrogen replacement therapy.

254 189 259

5 Benefits of combined regime of hormones may be perceptible to the patient within the first 6 weeks of administration, but variable responses can be expected. Typically, hormones are administered on a chronic basis to maintain health.

10

EXAMPLE 3

A combination of an androgenic compound and an estrogenic compound is administered to women who are post-menopausal to alleviate signs and symptoms associated with frailty, such as the loss of bone and muscle mass and function, reduced cognitive abilities and diminished energy.

Androgen: intramuscular injection of 150 mg testosterone enanthate every month. Testosterone enanthate is formulated to contain 200 mg per mL in sesame oil. In order to provide 150 mg of testosterone enanthate, the injected dose is 0.75 mL.

Estrogen: oral estrogens are given in a range of 0.3 to 3.0 mg/day.

255 790
260

5 Administration is performed as long as benefits of treatment are desired and deemed appropriate by the prescribing physician.

EXAMPLE 4

10 A combination of an androgenic compound and an estrogenic compound is administered to women with premature ovarian failure, e.g., women whose ovarian function permanently ceases prior to age 40.

15 Androgen: methyltestosterone is delivered by the buccal route at a dose of 1 mg/day to achieve an improvement in sexual function that is equi-efficacious to that produced by native testosterone at serum levels of about 50 to 300 ng/dL. The buccal tablet is a bilayer tablet consisting of a drug layer and a bio-adhesive layer (both 50 mg each).

20 The composition of the drug layer (in weight percent) is 2% methyltestosterone, 0.75 % magnesium stearate, 0.1% FD&C yellow #6, 24% Klucel HXF, and 73.15% mannitol. The composition of the bio-adhesive layer (in weight percent) is 69.25% polyethylene oxide, 30% carbomer 934P, and 0.75%

256 191
261

5 magnesium stearate. The adhesive side of the tablet is
affixed to the gingiva of the upper jaw and the drug side of
the tablet faces the overlying buccal mucosa. Drug is
absorbed transmucosally as the tablet dissolves over two
hours. The tablet is applied once daily after breakfast.

10 Estrogen: Estrace®, Bristol-Myers Squibb Co., an oral
micronized estradiol product in tablet form, is administered
at a dosage of 2 mg/day to alleviate menopausal symptoms and
prevent bone loss.

In addition a progestin, medroxyprogesterone acetate,
15 is orally administered at a dose of 5 mg/day for the last
ten days of each month to induce endometrial sloughing.

The treatment is administered until the patient reaches
about age 55, at which time it may be modified to other HRT
regimens.

20

These examples are intended to be indicative only of
regimens that can be utilized. Each regimen will preferably
be customized to meet the needs of the patient. While the
examples have been directed primarily to the delivery of an

257 192 262

5 androgenic steroid to provide needed supplementation based
on determination of a need for such, the administration will
be concurrent with the oral administration of estrogen
formulations.

Those skilled in the art will recognize, or be able to
10 ascertain using no more than routine experimentation, many
equivalents to the specific embodiments of the invention
described herein. Such equivalents are intended to be
encompassed by the following claims.

258 143 268

CLAIMS

1. A method of improving health in a woman comprising
coadministering effective amounts of estrogen and androgenic
steroids characterized in that said estrogen is administered
orally and said androgenic steroid is administered by a
parenteral means.

2. A method according to Claim 1 wherein said
androgenic steroid is administered in a dosage range of
about 50 and to about 1000 mcg/day, sufficient to maintain a
free androgenic steroid serum level equivalent to a free
testosterone serum level of between 0.5 and 15 pg/mL.

3. A method according to Claim 2 wherein said
androgenic steroid is administered in a dosage range of
about 300 to about 100 mcg/day.

259 1911
264

5 4. A method according to Claim 3 wherein said
androgenic steroid is administered in a dosage range of
about 550 to about 1000 mcg/day.

10 5. A method according to Claim 4 wherein said
androgenic steroid is administered in a dosage range of
about 550 to about 800 mcg/day.

15 6. A method according to Claim 2 or 3 wherein said
androgenic steroid is a member selected from the group
consisting of native testosterone, testosterone esters,
methyltestosterone, androstenedione, adrenosterone,
dehydroepiandrosterone, fluoxymesterone, methandrostenolone,
17 α -methylnortestosterone, nandrolone and its derivatives,
norethandrolone, dihydrotestosterone, oxymetholone,
20 stanozolol, ethylestrenol, oxandrolone, bolasterone and
mesterolone.

7. A method according to Claim 6 wherein said
androgenic steroid is a member selected from the group

5 consisting of testosterone, testosterone esters,
dihydrotestosterone and methyltestosterone.

8. A method according to Claim 7 wherein the
androgenic steroid is a member selected from the group
10 consisting of testosterone and testosterone esters,
dihydrotestosterone and methyltestosterone.

9. A method according to Claim 8 wherein said
androgenic steroid is testosterone.
15

10. A method according to Claim 7 wherein the
androgenic steroid is methyltestosterone.

11. A method according to Claim 7 wherein the
20 androgenic steroid is dihydrotestosterone.

12. A method according to Claim 2 or 3 wherein said
estrogen administered orally is in a dosage range of
equivalent to the dose response obtained from administering

260 145 265

5 conjugated estrogen in a dosage range of between 0.02 to 3.0
mg/day.

13. A method according to Claim 12 wherein said
estrogen administered orally is selected from a group
10 consisting of 17b-estradiol, α -estradiol, conjugated
estrogen, esterified estrogens, micronized estradiol, sodium
estrogen sulfate, ethinyl estradiol, estrone, other
estrogenic steroids and derivatives and esters thereof.

15 14. A method according to Claim 13 wherein said
estrogen administered orally is a conjugated estrogen.

15. A method according to Claim 13 wherein said
estrogen administered orally is a esterified estrogen.
20

16. A method according to Claim 13 wherein said
estrogen administered orally is a micronized estradiol.

17. A method according to Claim 2 or 3 wherein said

261 146
266

5 estrogen hormone administered orally is in the form of an
oral contraceptive.

18. A method according to Claim 2 or 3 wherein said
improvement of physiological health is manifest by one or
10 more of the following parameters: restoration or enhancement
of sexual desire, restoration or enhancement of stimulation
to sexual organs, restored or enhanced ability to achieve
orgasm, restoration or enhancement of pleasure in sexual
activity, restoration or enhancement of vital energy and
15 sense of well-being, enhancement in muscle tone, bone
mineral density, condition of skin and hair, and reduction
in vasomotor instability.

19. A method according to Claim 2 or 3 wherein
20 progesterone is administered concomitant with estrogen
administration.

20. A method according to Claim 2 or 3 wherein the
parenteral means is selected from the group consisting of

263 798 268

5 transdermal delivery means, means of topical administration to the skin, sublingual delivery means, transbuccal delivery means, transmucosal delivery means, intramuscular injection and subdermal implants.

10 21. A method according to Claim 20 wherein the parenteral means is selected from the group consisting of transdermal delivery means, intramuscular injection, and subdermal implants.

15 22. A method according to Claim 21 wherein the parenteral means is intramuscular injection.

23. A method according to Claim 21 wherein the parenteral means is subdermal implants.

20 24. A method according to Claim 20 wherein the parenteral means is a topical cream or gel.

264 199 269

5 25. A method according to Claim 20 wherein the
parenteral means is a transdermal device.

26. A method according to Claim 25 wherein the
transdermal device is a matrix type transdermal device.

10

27. A method of improving health in a woman receiving
oral estrogen in an oral estrogen regimen, comprising
administration of from about 50 to 1000 mcg/day of an
androgenic steroid by a parenteral means to achieve a free
15 testosterone serum level of from about 0.5 to about 15
pg/mL.

28. A method according to Claim 25 wherein the
delivering rate level of androgenic steroid is about 300 to
20 about 1000 mcg/day.

29. A method according to Claim 26 wherein the
delivering rate of the androgenic steroid is about 550 to
about 1000 mcg/day.

265 260 270

5 30. A method according to Claim 29 wherein the
delivering rate of the androgenic steroid is about 550 to
about 800 mcg/day.

10

0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
66
67
68
69
70
71
72
73
74
75
76
77
78
79
80
81
82
83
84
85
86
87
88
89
90
91
92
93
94
95
96
97
98
99
100

ABSTRACT OF THE DISCLOSURE

266 201 271

The invention provides methods for coadministration of oral estrogen and parenteral androgenic steroids to alleviate symptoms attributable to the deficiency or imbalance of estrogen and androgenic hormones in females. 10 Optionally, progestins are also administered. Deficiencies are indicated by women having diminished androgen production. The method of improving health in a woman comprises coadministering effective amounts of estrogen and 15 androgenic steroids characterized in that the estrogen is administered orally and the androgenic steroid is administered parenterally. Estrogen administered orally is in a dosage range equivalent to the dose response obtained from administering conjugated estrogens in a dosage range of 20 between 0.02 to 3.0 mg/day. The parenteral administration of androgenic steroid is in a dosage range equivalent to administering testosterone in a dose of about 50 to 1000 mcg/day.

267 202 272

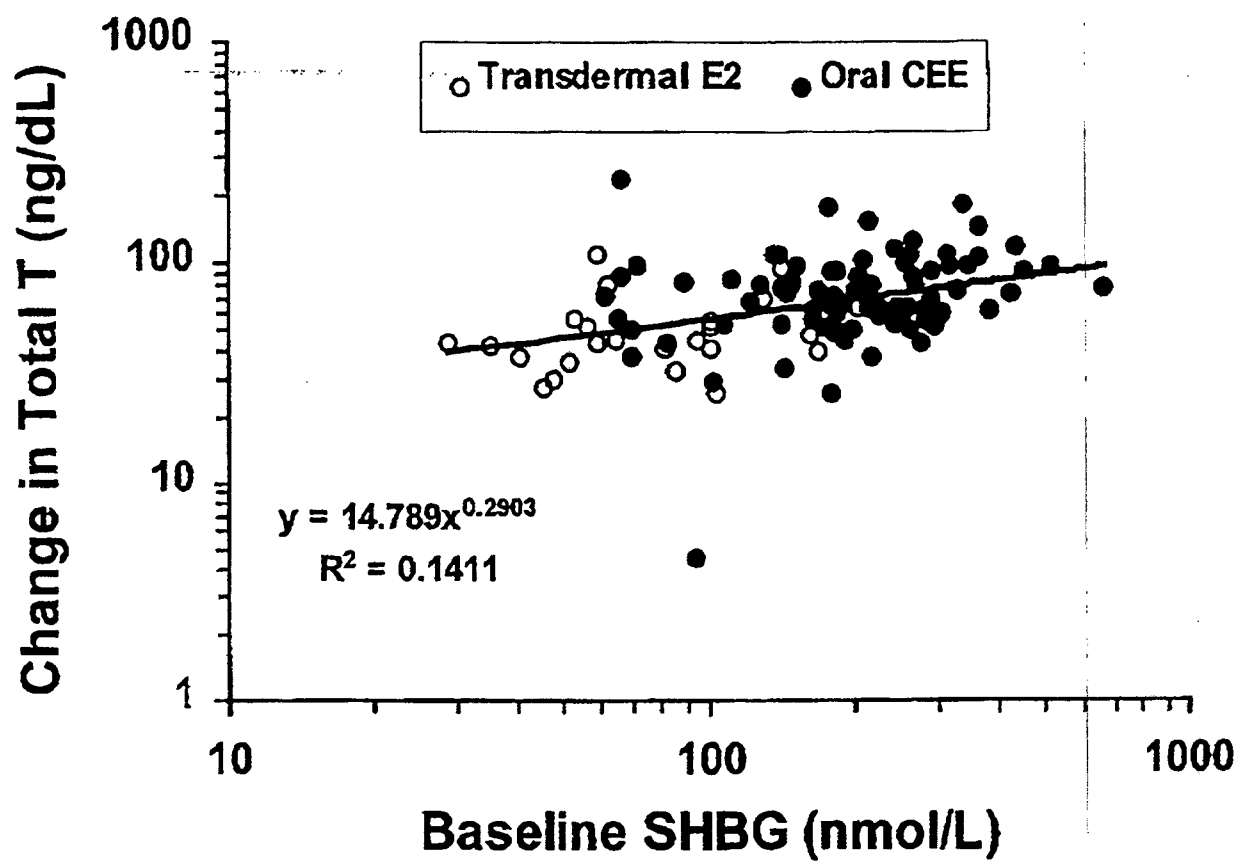


Figure 1

268 203 273

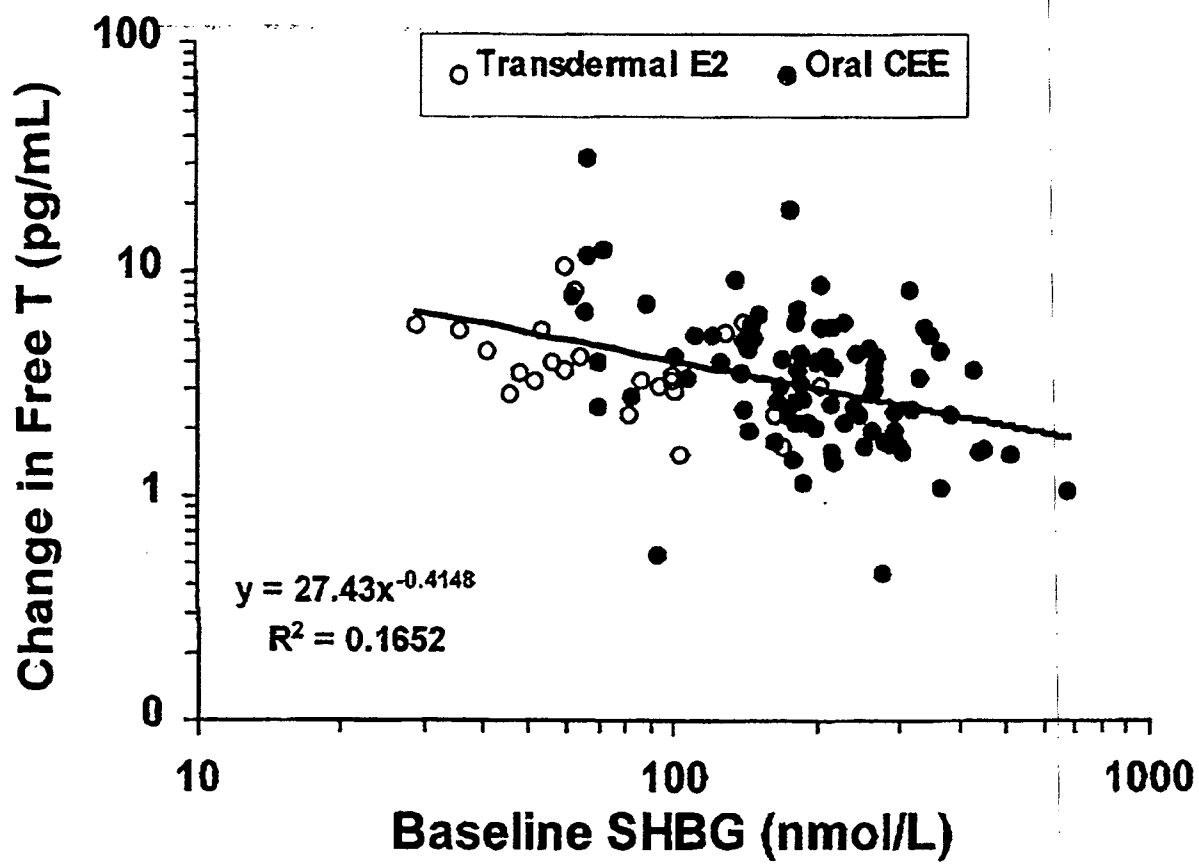


Figure 2

P-34305
269 275

LOS ESTADOS UNIDOS DE AMÉRICA

**A TODOS A QUIENES LOS PRESENTES DOCUMENTOS
PUDIERAN LLEGAR:**

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS

Oficinas de Patentes y Marcas de los Estados Unidos

28 de junio de 2000

**POR LA PRESENTE SE CERTIFICA QUE LA ANEXA AQUÍ ES UNA
COPIA VERDADERA TOMADA DE LOS REGISTROS DE LA OFICINA DE
PATENTES Y MARCAS DE LOS ESTADOS UNIDOS, DE LOS
DOCUMENTOS DE LA SOLICITUD DE PATENTE ABAJO IDENTIFICADA
QUE SATISFACE LOS REQUERIMIENTOS PARA SERLE OTORGADA
UNA FECHA DE PRESENTACIÓN SEGÚN 35 USC 111.**

**NÚMERO DE SOLICITUD: 60/139,323
FECHA DE SOLICITUD: 11 de junio de 1999**

**Por la Autoridad del
COMISIONADO DE PATENTES Y MARCAS**

(Hay firma ilegible)
T. LAWRENCE
Oficial de Certificaciones

Hay sello seco que dice:
**OFICINA DE PATENTES Y MARCAS
ESTADOS UNIDOS DE AMÉRICA**

271 267
277

deshidroepiandrosterona, fluoximesterona, metandrostenolona, 17α -metilnostestosterona, nandrolona y sus derivados, noretandrolona, dihidrotestosterona, oximetolona, estanozolol, etilestrenol, oxandrolona, bolasterona y mesterolona.

- 5 7. Un método de acuerdo a la reivindicación 6 en donde dicho esteroide androgénico es un miembro seleccionado del grupo consistente de testosterona, ésteres de testosterona, dihidrotestosterona y metiltestosterona.
8. Un método de acuerdo a la reivindicación 7 en donde el esteroide
10 androgénico es un miembro seleccionado del grupo consistente de testosterona, dihidrotestosterona y ésteres de testosterona, dihidrotestosterona y metiltestosterona.
9. Un método de acuerdo a la reivindicación 8 en donde dicho esteroide androgénico es testosterona.
- 15 10. Un método de acuerdo a la reivindicación 7 en donde el esteroide androgénico es metiltestosterona.
11. Un método de acuerdo a la reivindicación 7 en donde el esteroide androgénico es dihidrotestosterona.
12. Un método de acuerdo a la reivindicación 2 ó 3 en donde dicho
20 estrógeno administrado oralmente está en un intervalo de dosis equivalente a la respuesta a la dosificación obtenida al administrar estrógeno conjugado en un intervalo de dosis de entre 0.02 a 3.0 mg/día.
13. Un método de acuerdo a la reivindicación 11 en donde dicho
25 estrógeno administrado oralmente es seleccionado del grupo consistente de 17β -estradiol, α -estradiol, estrógeno conjugado,

272

208
278

estrógenos esterificados, estradiol micronizado, estrógeno sulfato de sodio, etinil estradiol, estrona, otros esteroides estrogénicos y derivados y ésteres de los mismos.

14. Un método de acuerdo a la reivindicación 13 en donde dicho
5 estrógeno administrado oralmente es un estrógeno conjugado.
15. Un método de acuerdo a la reivindicación 13 en donde dicho estrógeno administrado oralmente es un estrógeno esterificado.
16. Un método de acuerdo a la reivindicación 13 en donde dicho estrógeno administrado oralmente es un estradiol micronizado.
- 10 17. Un método de acuerdo a la reivindicación 2 ó 3 en donde dicha hormona estrógeno administrada oralmente está en la forma de un anticonceptivo oral.
18. Un método de acuerdo a la reivindicación 2 ó 3 en donde dicho
15 mejoramiento de salud fisiológica es manifestado por uno ó más de los siguientes parámetros: restauración ó mejoría del deseo sexual, restauración ó mejoría de la estimulación a los órganos sexuales, restauración o mejoría de la habilidad para alcanzar orgasmos, restauración ó mejoría del placer en la actividad sexual, restauración ó
20 mejoría de la energía vital y sentido de bienestar, mejoría en el tono muscular, en la densidad mineral del hueso, en la piel y el cabello, y reducción en la inestabilidad vasomotora.
19. Un método de acuerdo a la reivindicación 2 ó 3 en donde la progesterona es administrada concomitantemente con la administración de estrógeno.
- 25 20. Un método de acuerdo a la reivindicación 2 ó 3 en donde el medio parenteral es seleccionado del grupo consistente de medios de

273 25 22

liberación transdérmica, medios de administración tópica a la piel, medios de liberación sublingual, medios de liberación transbucal, medios de liberación transmucosal, inyección intramuscular e implantes subdérmicos.

- 5 21. Un método de acuerdo a la reivindicación 20 en donde el medio parenteral es seleccionado del grupo consistente de medio de liberación transdérmica, inyección intramuscular, e implante subdérmico.
22. Un método de acuerdo a la reivindicación 21 en donde el medio parenteral es inyección intramuscular.
- 10 23. Un método de acuerdo a la reivindicación 21 en donde el medio parenteral es implante subdérmico.
24. Un método de acuerdo a la reivindicación 20 en donde el medio parenteral es un gel ó crema tópica.
25. Un método de acuerdo a la reivindicación 20 en donde el medio
- 15 parenteral es un dispositivo transdérmico.
26. Un método de acuerdo a la reivindicación 24 en donde la inyección transdérmica es una matriz de tipo dispositivo transdérmico.
27. Un método de mejoramiento de la salud en una mujer que recibe estrógeno oral en un régimen de estrógeno oral, que comprende
- 20 administración de aproximadamente 50 a 1000 mcg/día de un esteroide androgénico por un medio parenteral para alcanzar un nivel total de testosterona en el suero de aproximadamente 0.5 a aproximadamente 15 pg/mL.
28. Un método de acuerdo a la reivindicación 25 en donde el nivel de
- 25 rata de liberación del esteroide androgénico es aproximadamente 300 a aproximadamente 1000 mcg/día.

271 210 20

29. Un método de acuerdo a la reivindicación 26 en donde el nivel de
rata de liberación del esteroide androgénico es aproximadamente 550 a
aproximadamente 1000 mcg/día.

30. Un método de acuerdo a la reivindicación 29 en donde la rata de
5 liberación del esteroide androgénico es aproximadamente 550 a
aproximadamente 800 mcg/día.



Clarke, Modet & Co.

COLOMBIA
E-MAIL: clarkemodet@clarkemodet.com.co
SANTAFÉ DE BOGOTÁ, A.A. 92397

275 285

SUPERINDUSTRIA Y COMERCIO
Radicación : 00043097 00000002
Fecha (AMD): 2000-10-03 16:45:50
Trámite : 022 PATENTES D 1 REGISTRO/ 467 SOLICITUD
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Folios: 2

SEÑORES
DIVISION DE NUEVAS CREACIONES
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
E. S. D.

COD:013

RE.: SOLICITANTE: WATSON PHARMACEUTICALS INC.
SOLICITUD N°. 00043097
PATENTE: ADMINISTRACIÓN DE ESTEROIDES ANDROGENICOS NO
ORALES A MUJERES
PRIORIDADES: US/138,851; 60/138,854; 60/139,323 DE JUNIO 11,
1999
FECHA DE SOLICITUD: JUNIO 9 DE 2.000

ASUNTO: SOLICITUD DE PRÓRROGA DEL TÉRMINO

DILIA RODRIGUEZ D'ALEMAN, en mi condición de apoderada de la sociedad solicitante en el expediente de la referencia, atentamente solicito a usted se me conceda **una prórroga del término**, fijado mediante Auto notificado 24 de Agosto de 2.000, que vence 5 de octubre de 2.000, para presentar los documentos faltantes y aclaraciones requeridas por el examinador oficial en la referida solicitud.

Fundamento mi solicitud en el artículo 22 de la Decisión 344 de 1993 del Acuerdo de Cartagena.

Anexo, el recibo de pago para efectos de lo anterior, y agradezco su atención.

Señor Jefe,

DILIA RODRIGUEZ D'ALEMAN
LCD/srr
P-343

276 282

Industria y Comercio

SUPERINTENDENCIA

SUPERINDUSTRIA Y COMERCIO

Radicacion: 00043097 00000002

Folios: 2

Fecha (AMD): 2003-10-03 16:45:58

Tramite: 032 PATENTES D 1 REGISTRO/ 467 SOLICITUD

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

ACORDADO RESOLUCION DE DATA 01/2003
SEPTIEMBRE 7 DE 2000

***** D E M O N S T R A T I V O *****

DEPOSITANTE	TIPO DE DERECHO	DANOS	CONTRATO	CLASE DE MARCA	FECHA DE DEPÓSITO	VALOR DE DEPÓSITO
ELABORADOR Y CO. COLOMBIANOS	DANOS ORDINARIOS	DEPOSITO		150.000.000	07/07/00	200.000.000

***** D E M O N S T R A T I V O *****

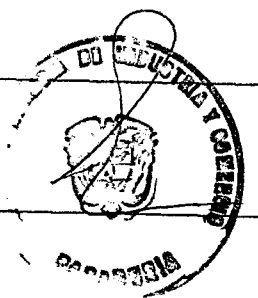
CANT. DEPOSITOS	CONCEPTO	TOTAL CONCEPTO
-----------------	----------	----------------

1. 500.000.000. 000.000.000 DE TERMINOS	31. 000.000.000.000.000 DE TERMINOS	50.000.000.000.000.000
TOTAL:		50.000.000.000.000.000

CONCEPTO CINCUENTA MIL PESOS

RESPONSABLE:

REGISTRO DE DATA APLICADO AL EXPEDIENTE NO.



Carrera 13 No. 27-00 Pisos 5 y 10
Conmutador: 334 12 21
Fax: 281 31 25
e-mail: info@sic.gov.co
Santa Fe de Bogotá, D.C., Colombia



Clarke, Modet

COLOMBIA
E-MAIL: clarkemodet@clarkem
SANTAFÉ DE BOGOTÁ, A.

277 7 283
SUPERINDUSTRIA Y COMERCIO

Radicación : 00043097

Fecha (A.D.): 2000-11-21/16:55:37

Folios: 10

Trámite : 002 PATENTES D

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

SEÑORES
DIVISION DE NUEVAS CREACIONES
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
E. S. D.

COD:008

RE.: SOLICITANTE: WATSON PHARMACEUTICALS INC.
SOLICITUD N°. 00043097 ✓
PATENTE: ADMINISTRACIÓN DE ESTEROIDES ANDROGENICOS NO
ORALES A MUJERES
PRIORIDADES: US/138,851; 60/138,854; 60/139,323 DE JUNIO 11,
1999
FECHA DE SOLICITUD: JUNIO 9 DE 2.000

ASUNTO CONTESTACIÓN AUTO

DILIA RODRÍGUEZ D'ALEMAN, en mi condición de apoderada de la sociedad
solicitante por el presente escrito doy respuesta a su auto notificado por estado de 24
de Agosto de 2.000 del cual solicité una prórroga el 3 de Octubre de 2.000, sometiendo
a su consideración los siguientes documentos y aclaraciones:

DOCUMENTOS:

1. Documento de poder, debidamente legalizado hasta por Cónsul de Colombia
en el país de origen.
2. Traducción al español, junto con la certificación del carácter de tal del
traductor oficial, expedida por el Ministerio de Relaciones Exteriores.
3. Las copias certificadas de las prioridades junto con sus traducciones al
español fueron presentadas en Septiembre 6 de 2.000, estando dentro del
término que exige el Convenio de Paris, toda vez que la solicitud fue
presentada el 9 de Junio de 2.000.

ACLARACIONES:

En las objeciones del examinador Oficial nos requiere presentar el arte final de la
fórmula característica.



Clarke, Modet & Co.

COLOMBIA

E-MAIL: clarkemodet@clarkemodet.com.co
SANTAFÉ DE BOGOTÁ, A.A. 92397

A este respecto me permito manifestar que la patente no tiene dibujo más característico que represente la invención, por lo tanto no presento arte final.

En el evento que resultara alguna discrepancia de carácter técnico, manifiesto expresamente que el solicitante mantiene interés en la solicitud por lo que quedo a disposición de atender a las observaciones formales y técnicas que su Despacho requiera antes o durante el examen de fondo, evitando el archivo de la solicitud.

Señor Jefe,

DILIA RODRÍGUEZ D'ALEMAN

LCD/srr

P. 343

279

285

STATE OF UTAH



OFFICE OF THE LIEUTENANT GOVERNOR

NOTARY PUBLIC CERTIFICATION

State of Utah)

ss.

United States of America)

I, OLENE S. WALKER, Lieutenant Governor of the State of Utah and custodian of the Great Seal of the State, do hereby certify that

JANN KNIGHT

whose notarization appears on the annexed instrument, was on the date thereof a duly appointed and qualified Notary Public in and for the State of Utah.



IN WITNESS WHEREOF, I have hereunto set my hand and affixed the Great Seal of the State of Utah, at Salt Lake City, this 8th day of November, A.D. 2000.

Olene S. Walker

Olene S. Walker
Lieutenant Governor

21 NOV 2000

