DHEA COMPOSITIONS FOR TREATING MENOPAUSE

FIELD OF THE INVENTION

[001]. The present invention provides novel ways of administering and dosing dehydroepiandrosterone (DHEA) in order to take advantage of positive androgenic effects (for example in the vaginal layers lamina propia and/or the layer muscularis), without undesirably causing systemic estrogenic effects. In addition to DHEA, other sex steroid precursors may be used (*e.g.*, dehydroepiandrosterone-sulfate, androst-5-ene-3β,17β-diol, and 4-androstene-3,17-dione).

BACKGROUND OF THE RELATED ART

[002]. Many hormone-related therapies are known. For example, many provide the sex steroids estrogen or androgen systemically and/or to target tissue. In addition to direct administration of androgens and/or estrogens, sex steroid precursors that can be converted to estrogen and/or androgen in a given tissue have also been used for many conditions. Both androgens and estrogens can be beneficial in some contexts and detrimental in others. That depends *inter alia* on the tissue being targeted, the specific needs presented by a patient, and the extent to which non-targeted tissue may be affected. Some therapies, though targeted, can still have undesirable activity elsewhere in the body (e.g. where local administration of the pharmaceutical agent nonetheless results in increased systemic presence of either the pharmaceutical or one of its metabolites. Also, the mechanism of action has not always been fully understood, especially the relative contributions of androgens and estrogens.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. The use of a sex steroid precursor which is dehydroepiandrosterone, dehydroepiandrosterone-sulfate, androst-5-ene-3β,17β-diol, or 4-androsten-3,17-dione in the manufacture of a medicament for treating or reducing the likelihood of acquiring a symptom or disease due to the menopause in postmenopausal women,

wherein said symptom or disease due to the menopause is: osteoporosis, hypogonadism, diminished libido, skin atrophy, connective tissue disease, urinary incontinence, breast cancer, endometrial cancer, ovarian cancer, uterine cancer, hot flashes, vasomotor symptoms, loss of muscle mass, insulin resistance, fatigue, vaginal pruritis, vaginal bleeding at sexual activity, loss of compactness of collagen fibers of the vaginal wall, or low muscularis thickness of the vaginal wall;

wherein said medicament comprises as active ingredient the sex steroid precursor in an amount effective to increase the level of circulating androgen metabolites consisting of androsterone glucuronide (ADT-G), androstane-3α,17β-diol-3-glucuronide (3α-diol-3G) and androstane-3α,17β-diol-17-glucuronide (3α-diol-17G), as part of a combination therapy with a therapeutically effective amount of a Selective Estrogen Receptor Modulator in order to decrease the risk of breast and uterine cancer normally present in postmenopausal women and to prevent bone loss, fat accumulation and diabetes type 2;

and wherein said therapy excludes any use of estrogen.

2. The use of claim 1, wherein the symptom or disease due to the menopause is osteoporosis.

3. The use of claim 1, wherein the symptom or disease due to the menopause is hypogonadism.

4. The use of claim 1, wherein the symptom or disease due to the menopause is diminished libido.

5. The use of claim 1, wherein the symptom or disease due to the menopause is skin atrophy.

6. The use of claim 1, wherein the symptom or disease due to the menopause is connective tissue disease.

7. The use of claim 1, wherein the symptom or disease due to the menopause is urinary incontinence.

8. The use of claim 1, wherein the symptom or disease due to the menopause is breast cancer.

9. The use of claim 1, wherein the symptom or disease due to the menopause is endometrial cancer.

10. The use of claim 1, wherein the symptom or disease due to the menopause is ovarian cancer.

11. The use of claim 1, wherein the symptom or disease due to the menopause is uterine cancer.

12. The use of claim 1, wherein the symptom or disease due to the menopause is hot flashes.

13. The use of claim 1, wherein the symptom or disease due to the menopause is vasomotor symptoms.

14. The use of claim 1, wherein the symptom or disease due to the menopause is loss of muscle mass.

15. The use of claim 1, wherein the symptom or disease due to the menopause is insulin resistance.

16. The use of claim 1, wherein the symptom or disease due to the menopause is fatigue.

17. The use of claim 1, wherein the symptom or disease due to the menopause is vaginal pruritis.

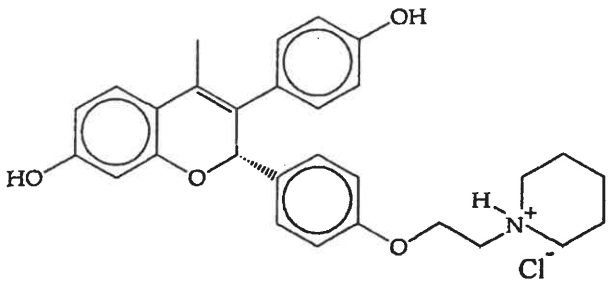
18. The use of claim 1, wherein the symptom or disease due to the menopause is vaginal bleeding at sexual activity.

19. The use of claim 1, wherein the symptom or disease due to the menopause is loss of compactness of collagen fibers of the vaginal wall.

20. The use of claim 1, wherein the symptom or disease due to the menopause is low muscularis thickness of the vaginal wall.

21. The use of any one of claims 1 to 20, wherein the Selective Estrogen Receptor Modulator has the following chemical structure:

Acolbifene (EM-652.HCl; EM-1538)



22. The use of any one of claims 1 to 21, wherein the sex steroid precursor is formulated to be administered on the skin.

23. The use of claim 22, wherein the therapeutic amount of sex steroid precursor is formulated to be administered by means of a topical formulation which is a cream, lotion, gel, ointment or sustained release patch.

24. The use of any one of claims 1 to 21, wherein the sex steroid precursor is formulated to be administered orally.

25. The use of claim 24, wherein the therapeutic amount of sex steroid precursor is formulated to be administered by means of an oral formulation which is a capsule, plug capsule, pill, tablet, or syrup.

26. The use of any one of claims 22 to 25, wherein the therapeutic amount of sex steroid precursor is 200 mg per day or less.

27. The use of any one of claims 22 to 25, wherein the therapeutic amount of sex steroid precursor is 100 mg per day or less.

28. The use of any one of claims 22 to 25, wherein the therapeutic amount of sex steroid precursor is 50 mg per day or less.

29. The use of any one of claims 22 to 25, wherein the therapeutic amount of sex steroid precursor is 25 mg per day or less.

30. The use of any one of claims 1 to 21, wherein the sex steroid precursor is formulated to be administered intravaginally.

31. The use of claim 30, wherein the therapeutic amount of sex steroid precursor is 100 mg per day or less and more than 13 mg per day.

32. The use of claim 30 or 31, wherein the therapeutic amount of sex steroid precursor is formulated to be administered by means of a intravaginal formulation which is a cream, lotion, gel, ointment, ovule, suppository or ring.

33. The use of any one of claims 1 to 32, wherein said sex steroid precursor is dehydroepiandrosterone.

34. A pharmaceutical composition for treating or reducing the likelihood of acquiring a symptom or disease due to the menopause in postmenopausal women, comprising:

a) a sex steroid precursor which is dehydroepiandrosterone, dehydroepiandrosterone sulfate, androst-5-ene-3β,17β-diol, or 4-androstene-3,17-dione, in an amount effective to increase the level of circulating androgen metabolites consisting of androsterone glucuronide (ADT-G), androstane-3α,17β-diol-3-glucuronide (3α-diol-3G) and androstane-3α,17β-diol-17-glucuronide (3α-diol-17G); and

b) a selective estrogen receptor modulator in an amount effective to decrease the risk of breast and uterine cancer normally present in postmenopausal woman and to prevent bone loss, fat accumulation and diabetes type 2;

wherein said composition is free of estrogen;

and wherein said symptom or disease due to the menopause is: osteoporosis, hypogonadism, diminished libido, skin atrophy, connective tissue disease, urinary incontinence,

breast cancer, endometrial cancer, ovarian cancer, uterine cancer, hot flashes, vasomotor symptoms, loss of muscle mass, insulin resistance, fatigue, vaginal pruritis, vaginal bleeding at sexual activity, loss of compactness of collagen fibers of the vaginal wall, or low muscularis thickness of the vaginal wall.

35. The pharmaceutical composition of claim 34, wherein the symptom or disease due to the menopause is osteoporosis.

36. The pharmaceutical composition of claim 34, wherein the symptom or disease due to the menopause is hypogonadism.

37. The pharmaceutical composition of claim 34, wherein the symptom or disease due to the menopause is diminished libido.

38. The pharmaceutical composition of claim 34, wherein the symptom or disease due to the menopause is skin atrophy.

39. The pharmaceutical composition of claim 34, wherein the symptom or disease due to the menopause is connective tissue disease.

40. The pharmaceutical composition of claim 34, wherein the symptom or disease due to the menopause is urinary incontinence.

41. The pharmaceutical composition of claim 34, wherein the symptom or disease due to the menopause is breast cancer.

42. The pharmaceutical composition of claim 34, wherein the symptom or disease due to the menopause is endometrial cancer.

43. The pharmaceutical composition of claim 34, wherein the symptom or disease due to the menopause is ovarian cancer.

44. The pharmaceutical composition of claim 34, wherein the symptom or disease due to the menopause is uterine cancer.

45. The pharmaceutical composition of claim 34, wherein the symptom or disease due to the menopause is hot flashes.

46. The pharmaceutical composition of claim 34, wherein the symptom or disease due to the menopause is vasomotor symptoms.

47. The pharmaceutical composition of claim 34, wherein the symptom or disease due to the menopause is loss of muscle mass.

48. The pharmaceutical composition of claim 34, wherein the symptom or disease due to the menopause is insulin resistance.

49. The pharmaceutical composition of claim 34, wherein the symptom or disease due to the menopause is fatigue.

50. The pharmaceutical composition of claim 34, wherein the symptom or disease due to the menopause is vaginal pruritis.

51. The pharmaceutical composition of claim 34, wherein the symptom or disease due to the menopause is vaginal bleeding at sexual activity.

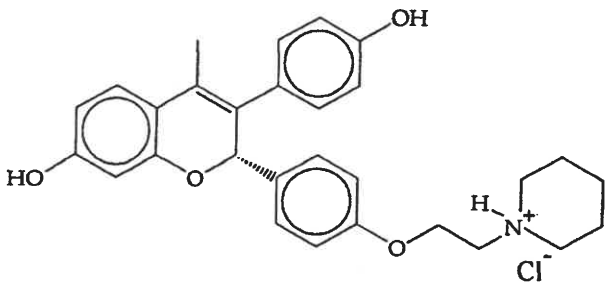
52. The pharmaceutical composition of claim 34, wherein the symptom or disease due to the menopause is loss of compactness of collagen fibers of the vaginal wall.

53. The pharmaceutical composition of claim 34, wherein the symptom or disease due to the menopause is low muscularis thickness of the vaginal wall.

54. The pharmaceutical composition of any one of claims 34 to 53, wherein the sex steroid precursor is dehydroepiandrosterone and the selective estrogen receptor modulator is acolbifene.

55. The pharmaceutical composition of claim 54, wherein the Selective Estrogen Receptor Modulator has the following chemical structure:

Acolbifene (EM-652.HCl; EM-1538)



56. The pharmaceutical composition of any one of claims 34 to 55, which is formulated to be administered on the skin.

57. The pharmaceutical composition of claim 56, which is in the form of a cream, lotion, gel, ointment or sustained release patch.

58. The pharmaceutical composition of any one of claims 34 to 55, which is formulated to be administered orally.

59. The pharmaceutical composition of claim 58, which is in the form of a capsule, plug capsule, pill, tablet, or syrup.

60. The pharmaceutical composition of any one of claims 56 to 59, wherein the therapeutic amount of sex steroid precursor is 200 mg per day or less.

61. The pharmaceutical composition of any one of claims 56 to 59, wherein the therapeutic amount of sex steroid precursor is 100 mg per day or less.

62. The pharmaceutical composition of any one of claims 56 to 59, wherein the therapeutic amount of sex steroid precursor is 50 mg per day or less.

63. The pharmaceutical composition of any one of claims 56 to 59, wherein the therapeutic amount of sex steroid precursor is 25 mg per day or less.

64. The pharmaceutical composition of any one of claims 34 to 55, which is formulated to be administered intravaginally.

65. The pharmaceutical composition of claim 64, wherein the therapeutic amount of sex steroid precursor is 100 mg per day or less and more than 13 mg per day.

66. The pharmaceutical composition of claim 64 or 65, which is in the form of a cream, lotion, gel, ointment, ovule, suppository or ring.

67. The pharmaceutical composition of any one of claims 34 to 66, wherein said sex steroid precursor is dehydroepiandrosterone.

68. A kit for treating or reducing the likelihood of acquiring a symptom or disease due to the menopause in postmenopausal women, comprising:

a) a formulation containing a sex steroid precursor which is dehydroepiandrosterone, dehydroepiandrosterone-sulfate, androst-5-ene-3β,17β-diol, or 4-androsten-3,17-dione, in an amount effective to increase the level of circulating androgen metabolites consisting of androsterone glucuronide (ADT-G), androstane-3α,17β-diol-3-glucuronide (3α-diol-3G) and androstane-3α,17β-diol-17-glucuronide (3α-diol-17G);

b) a formulation containing a selective estrogen receptor modulator in an amount effective to decrease the risk of breast and uterine cancer normally present in postmenopausal women and to prevent bone loss, fat accumulation and diabetes type 2; and

c) instructions for the use thereof;

wherein said kit is free of estrogen;

and wherein said symptom or disease due to the menopause is: osteoporosis, hypogonadism, diminished libido, skin atrophy, connective tissue disease, urinary incontinence, breast cancer, endometrial cancer, ovarian cancer, uterine cancer, hot flashes, vasomotor symptoms, loss of muscle mass, insulin resistance, fatigue, vaginal pruritis, vaginal bleeding at sexual activity, loss of compactness of collagen fibers of the vaginal wall, or low muscularis thickness of the vaginal wall.

69. The kit of claim 68, wherein the symptom or disease due to the menopause is osteoporosis.

70. The kit of claim 68, wherein the symptom or disease due to the menopause is hypogonadism.

71. The kit of claim 68, wherein the symptom or disease due to the menopause is diminished

libido.

72. The kit of claim 68, wherein the symptom or disease due to the menopause is skin atrophy.

73. The kit of claim 68, wherein the symptom or disease due to the menopause is connective tissue disease.

74. The kit of claim 68, wherein the symptom or disease due to the menopause is urinary incontinence.

75. The kit of claim 68, wherein the symptom or disease due to the menopause is breast cancer.

76. The kit of claim 68, wherein the symptom or disease due to the menopause is endometrial cancer.

77. The kit of claim 68, wherein the symptom or disease due to the menopause is ovarian cancer.

78. The kit of claim 68, wherein the symptom or disease due to the menopause is uterine cancer.

79. The kit of claim 68, wherein the symptom or disease due to the menopause is hot flashes.

80. The kit of claim 68, wherein the symptom or disease due to the menopause is vasomotor symptoms.

81. The kit of claim 68, wherein the symptom or disease due to the menopause is loss of muscle mass.

82. The kit of claim 68, wherein the symptom or disease due to the menopause is insulin resistance.

83. The kit of claim 68, wherein the symptom or disease due to the menopause is fatigue.

84. The kit of claim 68, wherein the symptom or disease due to the menopause is vaginal pruritis.

85. The kit of claim 68, wherein the symptom or disease due to the menopause is vaginal bleeding at sexual activity.

86. The kit of claim 68, wherein the symptom or disease due to the menopause is loss of compactness of collagen fibers of the vaginal wall.

87. The kit of claim 68, wherein the symptom or disease due to the menopause is low muscularis thickness of the vaginal wall.

88. The kit of any one of claims 68 to 87, wherein the sex steroid precursor is dehydroepiandrosterone and the selective estrogen receptor modulator is acolbifene.