

(19)
(12)

(KR)
(A)

(51) 。 Int. Cl. ⁷

A61K 31/56

A61K 31/568

A61K 31/565

(11)

(43)

2002 - 0011437

2002 02 08

(21) 10 - 2001 - 7015926

(22) 2001 12 11

2001 12 11

(86) PCT/US2000/15834

(86) 2000 06 09

(87)

WO 2000/76522

(87)

2000 12 21

(81)

가

가

가

가

가

AP ARIPO : 가

EA : 가

EP : 가

OA OAPI : 가

(30) 60/138,851 1999 06 11 (US)

60/138,854 1999 06 11 (US)

60/139,323 1999 06 11 (US)

$$(71) \quad ,$$

$$, \quad 91718 - 1900, \quad , \quad 1900, \quad 311$$

(72)

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,	45140,	,	6773
,		.	
,	84124,	,	4641

(74)

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(54)

-

(SHBG)

-

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,

. 1

(300mcg/day)

SH

BG

. 2

(300mcg/day)

SHBG

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1

: 60/138,851, 60/138,854, 60/139,323

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June 11, 1999

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(,)

(SHBG)

. SHBG

SHBG -

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, SHBG

. SHBG

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, (, -)

. SHBG

SHBG

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SHBG

(SHBG)

SHBG

, 17 -

가

15 1000ng/dl

0.5 30pg/Ml

1 70ng/dl 가

50mcg/day

17 -

, 17 -

(SERM),

0.2 30mg/day

가

가

1 (300m
cg/day) SHBG

2 (300m
cg/day) SHBG

A.

(referent)가

가

가

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17 -

" IUPAC (17) - 17 -
- one,
th ed., (1996)

- 4 - en - 3 - one, Δ^4 - - 17 - ol - 3
Merck Index, entry no. 9322, page 1569, 12

" " "

. 17 - - , 17 - - , ,

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- 3, 17 - , - 3 - , - 17 - ,

- 3, 17 - , - 3 - , - 17 - ,

(SERMS), Eli Lilly Evista

? . (,), , .

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, , , .

th - Ayerst Laboratories Premarin 가 Wye
Estratab , Bristol Meyers Wquibb , Solvay Pharmaceuticals Estratab ?

" " SHBG" (SHBP) (TeBG) " (1; Dune et al., Trans port of Steroid Hormones: Binding of 21 Endogenous Steroids to Both Testosterone - Binding Globulin and Corticosteroid - Binding Globulin in Human Plasma, J. Clinical Endocrinology and Metabolism, Vol. 53:58 - 67(1983). SHBG (K) 1 (Dunn et al., 1981)

$$\begin{bmatrix} 1 \end{bmatrix}$$

	K(10 ⁶ /mole)
	1300
	1500
	29
	14
	66
	5500
	680
	4.3
	150
	8.8
17 -	9.9
	1600

 1×10^6 /mole

SHBG

SHBG (Rosner et al., Sex Hormone - Binding Globulin Mediates Steroid Hormone Signal Transduction at the Plasma Membrane, J. Steroid Biochem. Mol. Vol. 69:481 - 5(1999) ; Petra, P.H. The plasma Sex Steroid Binding Protein (SBP or SHBG). A Critical Review of Recent Developments on the Structure, Molecular Biology, and Function, J. Steroid Biochem. Mol. Biol., Vol. 40:735 - 53 (1991)). SHBG

(Khan et al., Radioimmunoassay for Human Testosterone - Estradiol - Binding Globulin. J. Clinical Endocrinology and Metabolism, Vol. 54:506 - 710(1982)).

SHBG	84 nmole/	,	36	185 nmole/	.	SHBG
,	,	,	,	HIV -	,	

(Bond et al., Sex Hormone Binding Globulin in Clinical Perspective, Acta. Obstet. Gynecol. Scand., Vol. 66:255 - 262 (1987); Millet et al. Transdermal Testosterone Administration in Women with Acquired Immunodeficiency Syndrome Wasting: A Pilot Study, J. of Clinical Endocrinology and Metabolism, Vol. 83:27172725(1998)).

가

" " , , , , .

" " , , , , , (vaginal ring), , , .

" " .

, , , , , , , .

" " " " " " , , .

가 , , .

U.S. Nos. 5,122,383 5,460,820 , .

(,) (LRS) .

(,) . LRS . LRS U.S. Nos. 4,849,224 4,983,395 , .

" " , " " , " " , () , , , , , " " " " .

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- " " .

" " " " " " " " .

" " " " " " - .

), SHBG (Dunn et al.).

, " (1) ; (2) ,
 ; (3) ,
 SHBG - .
 " - "

(RIA) . Endocrine Sciences, Inc. (Calabassas Hills, CA) RIA . Furuyama et al., Radioimmunoassay for Plasma Testosterone, Steroids. 1970; 16:415 - 428 RIA , 14
 Endocrine Sciences, Inc. 54.3ng/dl (Miller et al. 1988).

" " " /
 /
 (FT) .
 " 가 " , " 가 " SHBG
 . , " " () " ()
 가 (-) , - (3.6
 $\times 10^4$ /mole) (mole/) (Vermeulen et al., A Critical Evaluation of Simple Methods for the Estimation of Free Testosterone in Serum, J. of Clinical Endocrinology and Metabolism Vol. 84:3666 - 3672(1999)).
 7.6×10^{-4} mole/) , 22가 , 가
 SHBG , 23 가 .

가 , (Nankin et al. Daytime Titers of Testosterone, LG, Estrone, Estradiol, and Testosterone - Binding Protein: Acute Effects of LH - Releasing Hormone in Men, J. clinical Endocrinology Metabolism, Vol. 41:271 - 81(1975)).
 Endocrine Sciences, Inc. 가
 1.6 12.7ng/dl, 2 13ng/dl .

" " , " SHBG
 . " "

," " , " , " , RIA
 , SHBG, (Winters et al. The Analog Free Testosterone Assay: Are the Results in Men Clinically Useful?, clinical Chemistry Vo. 44 :2178 - 2182(1998)). , 가 (Mather et al., Free Plasma Testosterone Levels During the Normal Menstrual Cycle, J. Endocrinol Invest Vol. 8:437 - 41(1985); Vermeulen et al.(1999)).
 Endocrine Sciences, Inc. 1.3 6.8 pg/Ml, 2 7 pg/Ml .

가, Brief In
dex of Sexual Functioning for Women, (Taylor et al 1994); Derogatis Interview for Sexual Funtioning, De
rogatis, L., The Derogatis iInterview for Sexual Functioning (DISF/DISF - SR): an introductory report, J.
Sex. Marital Ther. Winter 23(4):291 - 304(1997), Derogatis et al., Psychological
assessment measure of human sexual functioning in clinical Trials, Int. J. Impot. Res., May 10 Suppl. 2:S
13 - 20(1998) 가, x -
(DEXA) Beck Depression Inventory (Beck et al 1
961), the Psychological General Well - being Index(Dupuy 1984),
(, , ,) Schimer ,
가 (Mathers et al. Menopause and Tear Function: The Influence of Prolactin and Sex Horm
ones on Human Tear Production, Cornea Vol. 17:353 - 8 (1998)). 가 - 가, CD
4+ CD8+ 가 (, ,) 가

SHBG " " , SHBG , SHBG Endocrine Scie
nces 가 84nmole/ . "
" SHBG , SHBG
SHBG . 가 , Endocrine Sciences
가 185nmole/
SHBG ,
SHBG .

SHBG, 225 nmole/ 가 100 nmole/

가

" "

' " "

,

가

,

-

가

가 , 0.5 15pg/Ml 0.5pg/Ml 15pg/Ml
0.5pg/Ml, 0.7pg/Ml, 1.0pg/Ml, 5.2pg/Ml, 11.6pg/Ml, 14.2pg/Ml - , 0.5 - 2.5
pg/Ml, 4.8 - 7.2pg/Ml, 6 - 14.9pg/Ml가 .

B.

Ebert, et al., U.S. 5,460,820

(Vermeulen et al. Metabolic Clearance Rate and Interconversion of Androgens and the Influence of the Free Androgen Fraction, J. Clinical Endocrinology and Metabolism Vol 48:320 - 326(1979); Longcope et al. Free Estradiol, Free Testosterone, and Sex Hormone - Binding Globulin in Perimenopausal Women, J. clinical Endocrinology and Metabolism Vo. 64:513 - 518(1987)).

Endocrine Sciences

Endocrine Sciences	SHBG	36	185 nmol/	.	,
	3.5				

[2]

()	No ERTn=19	E(2)(0.1mg/day) n=12	CEE(1.25mg/day) n=13
SHBG(nmol/)	85.6 ± 9.6	90.8 ± 12.9	226.3 ± 13.5
T (ng/dl)	57.2 ± 4.4	53.6 ± 7.2	70.8 ± 9.6
T (pg/ml)	4.60 ± 0.40	4.20 ± 0.70	2.56 ± 0.30

E2

T

CEE

2. SHBG (ERT) 2.5, SHBG 가, 30% .

가 2 40%

SHBG

가

가 SHBG

가 , SHBG

가 ,

SHBG
300mcg/day
가 1 2 SHBG
가 SHBG 가 SHBG
가 .

2 - SHBG 가 ,
 - SHBG (FT) 가 ,
 가 3 . 3 , FT 가
 () SHBG 가 . 가 , SHBG 700nm
 ol/ 15pg/M ℓ 가 2484 mcg/day
 가 .

[3]

SHBG(nmol/)	50	84	100	200	400	600	700
FT (pg/M ℓ)	가 (meg/day)						
1	55	69	74	98	131	155	166
2.5	139	172	185	246	328	388	414
5	277	344	369	492	656	777	828
10	554	687	739	985	1313	1553	1656
15	831	1031	1108	1477	1969	2330	2484

(ng/d ℓ) , 1 - 4
 . 4 ,
 SHBG 가 , 가 . 가 , SHBG 700 nmole/ (, 2484mcg/day)
 15pg/M ℓ 가 820ng/d ℓ .

[4]

SHBG(nmol/)	50	84	100	200	400	600	700
FT (pg/M ℓ)	(ng/d ℓ)						
1	9	12	14	23	37	49	55
2.5	21	31	35	57	92	123	137
5	43	61	69	113	184	245	273
10	85	123	139	226	368	490	547
15	128	184	208	339	553	736	820

2,3,4 , (,
) 가 .

SHBG
 , - SHBG /
 , 가 SH
 BG , SHBG
 . 가,
 , ,
 , / 가 SHBG
 , ,
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C.

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 .
 .
 , 0.5 30pg/M ℓ
 . 1 15pg/M ℓ
 , 1.
 3 6.8pg/M ℓ , 2 7pg/M ℓ
 . 3 10pg/M ℓ
 .
 , 1 70ng/d ℓ 가
 , 2 35ng/d ℓ 가
 , 2 13ng/d ℓ 가
 .
 , 15 1000ng/d ℓ
 . 85 1000ng/d ℓ
 ,
 100 1000ng/d ℓ
 .
 , 50mcg/day
 , 75 3000mcg/day
 ,
 600 3000 mcg/day
 , 700 3000 mcg/day
 .
 -
 .

U.

S. Nos. 5,122,383 5,153,997 , David W. Osborne and J

ill J. Henke, in their internet publication entitled Skin Penetration Enhancers Cited in the Technical Literature(: pharmtech.com/technical/osborne /osborne.htm)

가
가
(LRS)가

LRS) (

가 SHBG) 가 (,

가;
();
; 가 ;

0.2 30mg/day

1 1 2
()

, 21 7

(ERT)
50 - 3000mcg/day

가
가)
15 400ng/dl 0.5 15pg/Ml

1

20 55
0.625 2.5mg
2 300mcg/day
12 12 (Permarin ?)

Endocrine Sciences(Calabassas Hills, CA)

(15.5 254.3ng/dl), (1.7 33.7pg/Ml), 가 (2.3
71 ng/dl), (5 280 pg/Ml), (8 410pg/Ml)
62.7 563 nmol/ " " " "

92% , 48%
73%가

80ng/dl

, 78%가 6.8pg/Ml(Endocrine Sciences)
, 97%가 가 15pg/Ml

68%가 12.7ng/dl(Endocrine Sciences)

가 , 97%가 가 3

5ng/dl

2

:

1g 400mcg . 1g
0.5 - 15pg/Ml

30 - 250ng/dℓ .

, () ,
1 - 20pg/Mℓ

: 0.625mg/day ,
1.25mg/day ,
0.3mg/day .

6 가 ,

3

mg : 150mg . 150mg Mℓ 200
0.75Mℓ .

: 0.3 3.0mg/day .

가

4

, 40

: 1mg/day , 50 300ng/dℓ - (50mg)
() 2% , 0.75% , 0.

1% FD& C #6, 24% Klucel HXF, 73.15%
, 30% 934P, 0.75%

, 가 . 가 , .
1 .

: Estrace[®], Bristol - Myers Squibb Co.,
2mg/day .

, (sloughing)
10 5mg/day .

(57)

1.

(SHBG)
SHBG

2.

1

, 17 -

3.

1

15 1000ng/dl

4.

1

0.5 30pg/Ml

5.

1

1 70ng/dl 가

6.

1

50mcg/day

7.

1

8.

1

가

9.

8 , 0.2 3.0mg/day .

10.

8 , 17 - , 17 - , , , ,
(SERM), , , , .

11.

8 , 가 .

12.

8 , 가 .

13.

(SHBG) , .

14.

- (SHBG) .

15.

14 , SHBG 84nmole/ .

16.

14 , SHBG 185nmole/ .

17.

14 , SHBG 300nmole/ .

18.

14 17 , .

19.

27.

14 26 , 15 1000ng/dℓ

28.

27 , 85 1000ng/dℓ

29.

27 , 100 1000ng/dℓ

30.

14 26 , 0.5 30pg/Mℓ

31.

30 , 1 15pg/Mℓ

32.

30 , 3 10pg/Mℓ

33.

30 , 2 13pg/Mℓ

34.

14 26 , 1 70ng/dℓ 가

35.

34 , 2 35ng/dℓ 가

36.

34 , 2 13ng/dl 가 .

37.

14 26 , 50mcg/day .

38.

37 , 75 3000mcg/day .

39.

37 , 600 3000mcg/day .

40.

37 , 700 3000mcg/day .

41.

14 40 , - , .

42.

41 , , .

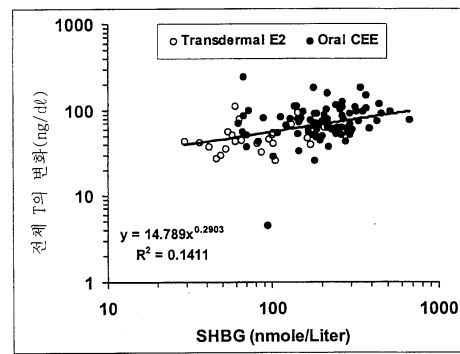
43.

41 , , , .

44.

14 43 (SHBG) , .

1



2

