

(19) (KR)
(12) (A)

(51) . Int. Cl. 7 (11) 2002 - 0011437
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A61K 31/568
A61K 31/565

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(22) 2001 12 11
2001 12 11
(86) PCT/US2000/15834 (87) WO 2000/76522
(86) 2000 06 09 (87) 2000 12 21

(81)	AP ARIPO	EA	EP	OA OAPI	60/138,851	1999 06 11	(US)
					60/138,854	1999 06 11	(US)
					60/139,323	1999 06 11	(US)

(71) ,
91718 1900 1900 311

(72) , - ,
, 45140, , 6773
,
, 84124, ,

(74)

:

(54)

(SHBG)

BG , 1 (300mcg/day) SH

2 (300mcg/day) SHBG

1

: 60/138,851, 60/138,854, 60/139,323 , June 11, 1999

SHBG - (,) (SHBG)

SHBG - " " , /

, SHBG SHBG (,)

, - (, -) SHBG SHBG ,

SHBG

(SHBG)

SHBG

17

15 1000ng/dl

0.5 30pg/Ml

1 70ng/dl

50mcg/day

(SERM),

0.2 30mg/day

가

1
cg/day) SHBG . (300m

2
cg/day) SHBG (300m

A.

(referent) 가

17

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

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

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

" (SHBP) (TeBG) "
 " " SHBG" (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)

[1]

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

. 1x10⁶ /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)).

- (Endocrine Sciences, Calabassas Hills, CA)

(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)).

(vaginal ring),

가

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

(,) (LRS)

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

), . . . , SHBG

(Dunn et al.).

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

SHBG -

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

$$\begin{aligned}
 & \text{FT} = \frac{\text{Total T}}{\text{SHBG}} = \frac{7.6 \times 10^{-4} \text{ mole/l}}{22 \text{ mole/l}} = 3.45 \times 10^{-4} \text{ mole/l} \\
 & \text{SHBG} = \frac{\text{Total T}}{\text{FT}} = \frac{7.6 \times 10^{-4} \text{ mole/l}}{3.45 \times 10^{-4} \text{ mole/l}} = 2.2 \text{ mole/l}
 \end{aligned}$$

가 , (Nankin et al.
Daytime Titers of Testosterone, LG, Estrone, Estradiol, and Testosterone - Binding Protein: Acute Effect
s 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
" " " " " (Winters et al.
, SHBG,
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(198
5); Vermeulen et al.(1999)). Endocrine Sciences, Inc.

가 (Laan 1998) 가 - 가 , Brief Index of Sexual Functioning for Women, (Taylor et al 1994); Derogatis Interview for Sexual Functioning, Derogatis, L., The Derogatis Interview 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 1961), the Psychological General Well - being Index(Dupuy 1984), . (, , , ,) Schimer , , , . 가 (Mathers et al. Menopause and Tear Function: The Influence of Prolactin and Sex Hormones on Human Tear Production, Cornea Vol. 17:353 - 8 (1998)). 가 - 가, CD 4+ CD8+ , 가 (, , , ,) 가

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

" " , 225 nmole/ SHBG 100 nmole/
SHBG , , , , "

가

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
 pg/Mℓ, 4.8 - 7.2pg/Mℓ, 6 - 14.9pg/Mℓ가

B.

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

50 500mcg/day
 15 80 ng/dℓ "

SHBG
 가

SHBG

(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)).

SHBG

가

SHBG

SHBG

가

가

2	300mcg/day	3	1	7
(ERT)		(CEE)	(E2)	
day			SHBG	
Endocrine Sciences				
3		(\pm SEM)	2	

Endocrine Sciences	SHBG	36	185 nmol/	,
	3.5			

[2]

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

E2

T

CEE

2	,	SHBG	2.5	,
		SHBG	(ERT)	
2		가,		

,	가	2	40%
		SHBG	
가	가		SHBG

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

[3]

SHBG(nmol/ L)	50	84	100	200	400	600	700
FT (pg/Ml)	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

SHBG
(ng/dl) 1 - . 4
SHBG 가 . 가 . 가 , SHBG 700 nmole/ (, 2484mcg/day
15pg/Ml 가 820ng/dl)

[4]

SHBG(nmol/ L)	50	84	100	200	400	600	700
FT (pg/Ml)							(ng/dl)
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

(

1

74

SHBG

SHBG / SHBG
SHBG / SHBG

C.

SHBG

0.5 30pg/Mℓ 1 15pg/Mℓ

3 6.8pg/Mℓ, 2 7pg/Mℓ 3 10pg/Mℓ

1.

1 70ng/dℓ 가 2 35ng/dℓ 가

2 13ng/dℓ 가

15 1000ng/dℓ 85 1000ng/dℓ

100 1000ng/dℓ

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

フ

(LRS) 가

LRS)

(

가 SHBG)

가

(

;();
;();
;();

가

가

0.2 30mg/day

1

1

2

()

21

7

,
50 - 3000mcg/day

가 (ERT)
가)
15 400ng/dℓ 0.5 15pg/Mℓ

1

20 55
0.625 2.5mg
2 300mcg/day
12 12 ,

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)
, 68%가 12.7ng/dℓ(Endocrine Sciences
, 97%가 가)
가 5ng/dℓ 3

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

150mg 200
mg 150mg Mℓ 0.75Mℓ
0.3 3.0mg/day

가

4

40

1mg/day 50 300ng/dℓ (50mg)
 (2%) 0.75% (0.69.25%)
 1% FD & C #6, 24% Klucel HXF, 73.15%
 , 30% 934P, 0.75%
 가 1
 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 , 7 , 7

12.

8 , 7 , 7

13.

(SHBG)

14.

(SHBG)

15.

14 , SHBG 84nmole/

16.

14 , SHBG 185nmole/

17.

14 , SHBG 300nmole/

18.

14 17 ,

19.

18

20.

18 19

(SERM),

21.

18 19

0.2 3.0mg/day

22.

18 21

23.

22

24.

22

25.

14 24

가

26.

14 25

17

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 , , ,

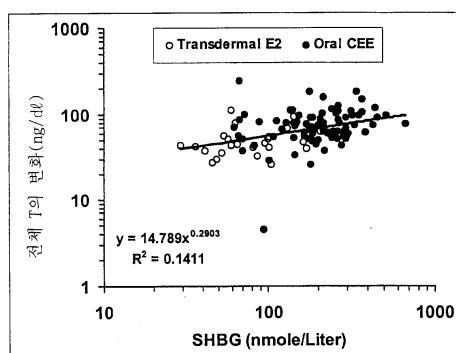
43.

41 , , ,

44.

14 43 (SHBG)

1



2

