

(19)
(12)

(KR)
(A)

(51) . Int. Cl.7
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C07C 401/00

(11)
(43)

10-2004-0101530
2004 12 02

(21)	10-2004-7016745		
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	2004 10 18		
(86)	PCT/US2003/012013	(87)	WO 2003/088976
(86)	2003 04 17	(87)	2003 10 30

(30)	10/127,005	2002 04 19	(US)
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(71)	53562	,	1600
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(72)	53705		3534
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53711	4917
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53726	24
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(74)

:

(54)

D /
D (ARVDD)
가 ARVDD :
, (1) 1 D , (2) 1,25-(OH) ₂ D ₃ (3) 1,25-(OH) ₂ D ₃ .

, , 1, 1,25-(OH)2D3 , 1,25-(O
H)2D3

, 1997 8 8	08/907,659(, , 5,869,473)	1998
5 29	09/086,969	2000 2 9

, 1995 4 3	08/415,488 (, 5,602,116)
1997 2 11	08/798,958 (, 5,707,980)
1997 8 8	08/907,660 .

$$\text{1,25-(OH)}_2\text{D}_3 \cdot \text{ARVDD} \quad \text{. ARVDD} \quad (3)$$

50% (PTH) PTH 가(30) D 80
 [: Lau, K.-H. W. and Baylink, D. J., *Calcif. Tissue Int.* 65: 295-306 (1999); Patnaungkul, S., et al., *J. Clinical Endocrinol. amp; Metab.* 85:11 4023-4027 (2000)].
 D [: Grady, D et al., *J. Clin. Endocrinol. amp; Metab.* 73:1111-1117 (1991); Bischoff, H.A. et al., *Arch. Phys. Med Rehabil.* 80:54-58 (1999); Theiler, R. et al., *Arch. Phys. Med. Rehabil.* 80:485-489 (1999); Bischoff, H.A. et al., *Histochem. J.* 33:19-24 (2001); Glerup, H. 'Investigations on the role of vitamin D in muscle function,' Ph.D. Thesis Aarhus Bone and Mineral Research Group, University of Aarhus, Denmark (1999); Gulbrahdsen, C.E. and Ross, R.L., 1994 9 27 5,350,745].

ARVDD , D 3가
 1,25- D 3 , 1,25- D 3 ; (2) 1,25- D 3 .
 D (1) 1 25- D 3 ; (3) 1,25- D 3 ,
 D / 25- D 3 , 1,25- D 3 [: Lau, K.-H. W. and Bayli
 nk, D. J., *Calcif. Tissue Int.* 65:295-306 (1999); Pattanaungkul, S et al., *J. Clinical Endocrinol. amp; Metab.* 85:11 4023-4027 (2000)].

[: Id.; Khaw, K.T. et al., Br. Med. J. 305-273-277 (1992)] 가 [: Eastell, R and Roggs, B.L., 'Vitamin D and Osteoporosis', Vitamin D, Feldman D, Glorieux FH, Pike JW (eds) Academic Press, San Diego, CA pp. 695-711 (1997); Chapuy, M.C. and Meunier, P.J., 'Vitamin D insufficiency in adults and the elderly', Vitamin D, Feldman D, Glorieux FH, Pike JW (eds) Academic Press, San Diego, CA pp. 679-693 (1997); Lau, K.-H. W. and Baylink, D.J., *supra*].

1 D , 1,25-(OH)₂D₃ , , D / 25-

1, 2 3 , , , . 1 ,
D , , , 1,25- 가 D 3
, 1,25- D 3 / 2 , 가
, , , . 3
, 2 . 3
, D , , , . 3
,

D [: Holick, M. F. et al., Proc. Natl. Acad. Sci. USA 68, 803-804 (1971); Jones, G. et al., Biochemistry 14, 1250-1256 (1975)] D [: Holick, M. F. et al., Science 180, 190, 191 (1973); Lam, H. Y. et al., Science 186, 1038-1040 (1974)]

[... : Ott, S. M. and Chesnut, C. H., Annals of Int. Med.; 110: 267-274 (1989); Gallagher, J. C. et al., Annals of Int. Med.; 113:649-655 (1990); Aloia, J. et al., Amer. J. Med. 84: 401-08 (1988); and Shiraki, M. et al., Endocrinol. Japan 32, 305-315 (1985)].

가
가 . 1 ,25- D₃ 0.5μg/
0.5μg/
[: Jensen, G. E. et al., Clin. Endocrinol. 16, 515-524 (1982); Christiansen, C.

, 1 - D₃ . 가, (Aloia) [: Aloia, J. et al., Amer. J. Med. 84:401-408 (1988)]. 1 - D₃ 1 ,25- D₃

1 - D₃ 1 .25- D₃ [: Gillespie, et al., Abstract, The Cochrane Library, issue 2, 2001; DeChant, K.L. and Goa, K.L., Drugs amp; Aging, 5(4):300-317 (1994); Ikeda, K Ogata, E., Mechanisms of Aging amp; Development 116:103-111 (2000); Tanizawa, T., Osteoporos. Int. 9:163-170 (1999); Civitelli, R., Calcif. Tissue 57:409-414 (1995); Parfitt, A.M., Drugs 36: 513-520 (1988); Thompson, S.P. et al., Brit. Edit. Soc. Bone Joint Surgery, 72:1053-1056 (1990); Sairanen, S. et al., Calcif. Tissue Int. 67:122-127 (2000); Haas, H.G., Horm. Metab. Res. 11:168-171(1979); Tilyard, M.W. et al., New England J. Med. 326:357-362 (1992); Aloia, J.F. et al., Am. J. Med. 84:401-408 (1988); Avioli, L., Calcif. Tissue Int. 65: 2392-294 (1999); Ori mi, H. et al., Calcif. Tissue Int. 54: 370-376 (1994); Sorensen, O.H. et al., Clinical Endocrinol. 7(Suppl.): 169S-175S (1997)]. 1 - D₃ 1 .25- D₃

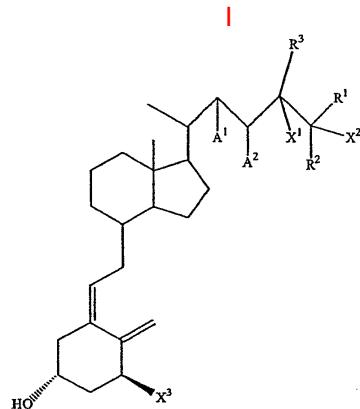
[: Zerwekh, J.E. et al., *J. Clin. Endocrinol Metab.* 56: 410-413 (1983); Nordin, B.E.C. et al., *Calcif. Tissue Int.* 65:307-310 (1999); Morris, H.A. et al., *Calcif. Tissue Int.* 49:240-243 (1991); Shiraishi, A. et al., *Calcif. Tissue Int.* 65:311-316 (1999); Silverberg, S.J. et al., *New England J. Med.* 320(5):277-281 (1989), Francis, R.M., *Calcif. Tissue Int.* 60: 111-114 (1997); Francis, R.M. et al., *Osteoporosis Int.* 6:284-290 (1996); Theiler, R. et al., *Int. J. Vit. Nur. Res.* 68: 36-41 (1998)].

, 2
, 300,000
, D (

D ₃	1	-	D	1	,25-(OH) ₂ D ₃	,	2	D ₃	1	-(OH)D ₃
.	.	.	D	1	,25-(OH) ₂ D ₃	,
,25-(OH) ₂ D ₃	,	,	.	.	.	,	.	.	.	,
.5 μ g	0.25	0.50 μ g/	(,)	0.5	1.0 μ g/	.	.	1.0
3	0.5	3.0 μ g	.	,	.	,	.	.	D	1
D ₃	.	.	1.0 μ g/	.	.	0.25	0.10 μ g/	.	-(OH)	1.

0 μ g/가 1,25-(OH)₂D₃, 1-(OH)D₃ D₃

D₃, 가 1.25mM
PTH
가, D, 가
2, 1-OH-D₃ 가, D₃ 가
[: Shiraishi, A et al., Calcif. Tissue Int. 65:292-294 (1999)].
가, D₃,
D, D₃,
_____,
(PTH), D
, D (ARVDD)
D 1, D, 1,25-(OH)₂D₃ 1,25-(OH)₂D₃ ARVD
가, , ARVDD
D, D (episodic) D, D
D, D
D, D (ARVDD) / ARVD
D, 25-(OH)₂D₃ : (1) 1, D, (2) 1,25-(OH)₂D₃ (3) 1, ARVDD
가
DD, PTH / ARV
, 1,25-(OH)₂D₃ / D
ARVDD, 1,25-(OH)₂D₃,
,
,
D
, ARVDD



I ,

A 1 A 2

C-22 C-23

R 1 R 2

, O- , O- , O- , O- , O- , O- [, R 1 , R 2 ;

C 3 -C 8

R 3 , O-

, O- , O- , O-

X 1

;

X 2

, R 1 R 2

;

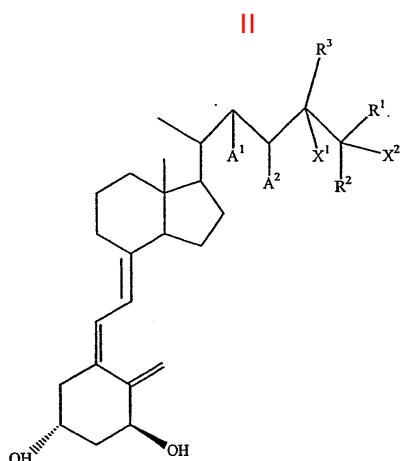
X 3

, X 1 , X 2 X 3

1 -

D

II



II ,

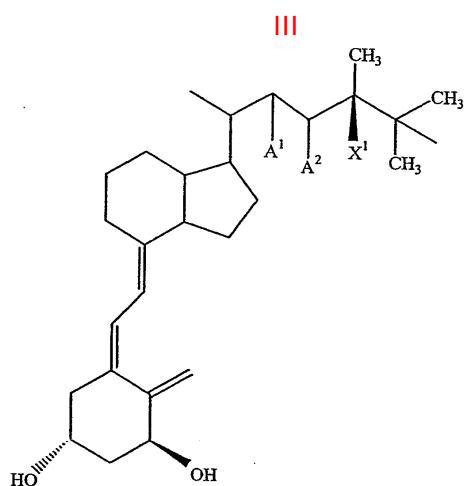
A 1 A 2

C-22 C-23

R 1 R 2

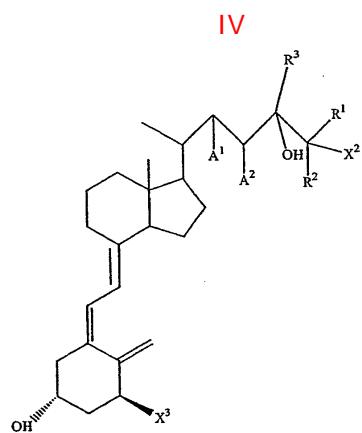
, O- , O- , O- , O- , O- [, R 1 , R 2 ,

], R¹ R² C₃-C₈ ;
 R³, O-, , , , , O-, O-, O-
 X¹ ;
 X² , R¹ R²
 R¹, R² R³ X² 가 , 1 - D
 III .



III ,
 A¹ A² ;
 X¹ .

24- D IV



IV ,

A 1 A 2 - C-22 C-23 ;
 R 1 R 2 , O- , O- , O- , O- , O- [, R 1 , R 2 ;
] , R 1 R 2 C 3 - C 8 ;
 R 3 , O- , O- , O- , O- , O- ;
 X 3 ;
 X 2 , R 1 R 2 .
 I IV 24- D , 25- D , 25- D
 1 - , 24- D 2 , 1 , 24- D 4 , 1 , 25- D 4 , 1
 , 25- D 2 , 1 , 24, 25- D 2 , 1 , 25- D 3 , 1
 24, 25- D 3 , 1 - D 2 , 1 - D 4 , 24
 - D 2 , 24- D 4 , 25- D 2 , 25- D 4
 .
 D 1 , 25- D 1 , 25- D 3 D 3
 , 1 , 25- D 3 , 25- 0.001 0.5 D
 1 D . D 3
 .
 가 , C-24 I IV 가 (, R S)
 가 , , 1 , 24(S)- D 2 (S)
 R) , 1 , 24(R)- D 4
 .
 I IV C 1 , C 24 D C 25 D III
 , , D 3
 D 3 , , 가 , , III
 가
 1 μ g 150 μ g D , 10 μ g/ 200 μ g/
 .
 ARVDD
 D ,
 D , D 2 , D 3 D 4 ()
 D ,
 .
 , 25- , 10 μ g , D 3 (100 μ g) , 1 -(OH)-D 3 (, 300 μ g) , 1
 , 20 μ g D ,
 1

가 (加糖)

(, 10 32)

가

r) . , (blister) .

(blister)

(dispense

가

()

(situ)

()

ARV
DD
가
,

I IV
D ,
가
,

2 가
,

()
,

2 가
,

1 가
,

) 가
,

D D
,

1 ,

[1]

			가
가 (mg/)	0.3-5.0	0.4-2.4	0.6-1.2
(mg/)	5-150	30-75	40-60
(IU/)	5-800	25-500	50-200
(mg/)	50-2000	100-1500	500-1000
(mg/)	250-2500	500-1500	750-1000
(μ g/)	5-200	20-100	30-50
(mg/)	0.1-2000	10-1500	100-1000
(mg/)	0.10-3000	1-250	2-100

, D , D , / ARVDD

D , [: 3,907,843 ; 4,195,027 ; 4,202,829 ; 4,234,495 ; 4,260,549 ; 4,555,364 ; 4,554,106 ; 4,670,190 ; 5,488,120 ; WO 94/05630, Strugnell et al., 310 Biochem. J. 233-241 (1995);]

가

1 -OH- D₂ 1 -OH- D₃

1 -(OH)D₃ 1 -(OH)D₂

. 114, 2043-2946 (1984)]. 1 -(OH)D₃ 1 -(OH)D₂ [: G. Sjoden et al., J. Nutr

[: G. Sjoden et al., Proc. Soc. Exp. Biol. Med. 178, 432-436 (1985)]. 5 15

1 -OH-D₂ 2 3

μg

1 (OH)D₂ 1 ,24-(OH)D₄ 가

PTH

1 ,25-(OH)D₃ 1 -(OH)D₃

, 1 ,24(S)-(OH)D₄ 가

가 1 -(OH)D₂

, 1 ,24(S)-(OH)D₂ 1 ,24(R)-(OH)D₃

D₃

1 ,24(R)-(OH)D₃

1:

1 -(OH)D₂ 15

: J. Bone Min. Res. ; 9: 607-614 (1994)].

0.7

55

75

LUNAR

('BMD')

1.05g/cm²

0.85 ± 0.17g/cm²

15 85

).

, 400 600mg

24

1 ,5 7

1

1 -(OH)D₂ 0.5μg/ 1.0, 2.0, 4.0, 5.0, 8.0 10.0μg/

가

1

24

1 -(OH)D₂ 가

가

1 -(OH)D₂

가

가

, 24

가

2:

1 -(OH)D₂

60

가

(DEXA)

0.7 1.05g/cm² L2-L3 BMD

x-

2 (1 -(OH)D₂)

104

700

900mg

24

가 $25\text{-}(\text{OH})\text{D}$, 1,25- $(\text{OH})_2\text{D}_3$ 50+%

mL. 3		PHT - 480 ± 21 pg/mL;			Ca - 8 ± 0.3 mg/mL			- 5.1 ± 0.2 mg/		
		PTH 2	68%, 74%	87%		2		PTH 4		
	33%		3%	.		PTH 1	-OH-D ₂		2	
4		$49 \pm 17\%$	$33 \pm 9\%$		(p<0.05).	2	4		(mg/dL)	$10.2 \pm$
0.4(p<0.05)		9.8 ± 0.2 (NS)	(NS),		(mg/dL)	5.4 ± 0.5	5.5 ± 0.8		(NS).	$1 - (\text{OH})D_2$
PTH가 130		3			,	1 - (OH)D ₂	2	4		PTH가
					(,	10.3	11.4mg/dL)		1 - (OH)D
2					.	1 - (OH)D ₂	4 μ g		4	6
4		가	PTH		,					, 5
/dL	6	1 - (OH)D ₂			,		10.0 ± 0.2 mg/dL			5.3 ± 0.2 mg
(OH)D ₂							PTH		8	1 -
			38%	.		1 - (OH)D ₂	가		2	

4:

12 - , D₃ (400IU/) 35 8

- $(\text{OH})\text{D}_2$ (u.i.d.: 3.0 $\mu\text{g}/\text{dL}$)
 가 (a) 7.0 mg/dL (b) (c) (d)

가 . 1 - (OH)D 2 가

5: 2

(ESRD)

120 ESRD()
 2 (multicenter), 20 (7)
 5, 2 (4)
) ()

$$\text{mg/dL} \quad , \quad 1.25\text{mM} \quad (\quad : \quad (\quad 3 \quad) \quad , \quad (\quad 1 \quad - (\text{OH})\text{D} \quad)_2 \quad . \quad . \quad . \quad) \quad 3 \quad 4\mu\text{g} \quad) \quad .$$

12 , PTH 130 240pg/mL , 2 12 PTH ()
 $1\text{-}(\text{OH})\text{D}_2$. (1) $1\text{-}(\text{OH})\text{D}_2$ ↑ PTH , (2) $1\text{-}(\text{OH})\text{D}_2$ ↑ ,
 D_2 ↑,

6: 2

PTH가

1, 25-(OH)D₃, PTH

1 34 (OH) D 가 iPTH

iBTH

2 3

8: 2 3 PTH가

2 PTH (: 1015 4706pg/mL . D)
 , - (OH)D₂ (10 μ g - 3 /) , 150 300pg/mL iPTH
 가 . 11 12 , 2 iPTH
 L , 9 iPTH 510pg/mL . iPTH 1000pg/m

9: ARVDD 1,25(OH)₂D₃ PTH가

ARVDD 가 1,25(OH)₂D₃ 50 80 PTH가 PTH ()
 m² 1,25(OH)₂D₃ () .
 2 , 30 1 1 -(OH)D₂ 20µg/ 500mg 1 가 , 30 .
 ; PTH , , ; , ,
 PTH 가 .

1 - (OH)D₂
PTH 가

10: ARVDD 1,25(OH)₂D₃ PTH가

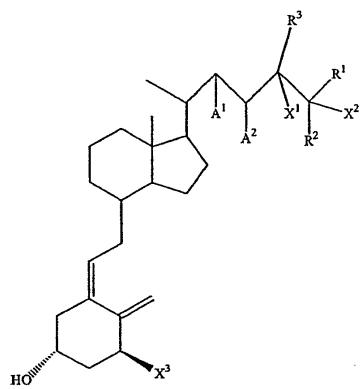
(57)

1. (PTH)
D ,

2. (ARVDD)
1 , D (ARVDD)
2 , (1) 1 D , (2) 1,25- D 3 (3) 1,25
D 3

3. , D 3

4. , D 1 D



I ,
 A 1 A 2 - C-22 C-23 ;
 R 1 R 2 , O- ;
] , R 1 R 2 C 3 - C 8 [, R 1 , R 2 ;
 R 3 , O- , O- , O- , O- , O- , O- ;
 X 1 ;
 X 2 , R 1 R 2 ;
 X 3 , X 1 , X 2 X 3 .

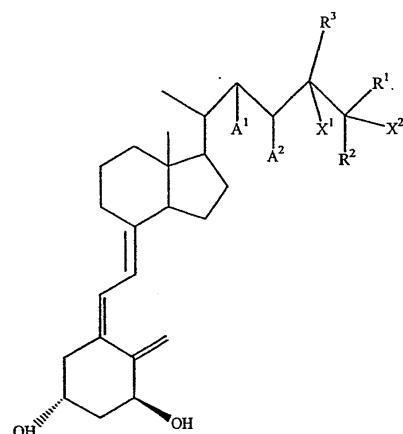
5.

3 , I D

6.

2 , D가 II 1 - D

II



II ,
 A 1 A 2 - C-22 C-23 ;
 R 1 R 2 , O- ;

], R¹ R²C₃-C₈

;

R³
, O-X¹X²

, O- , O- , O-

7.

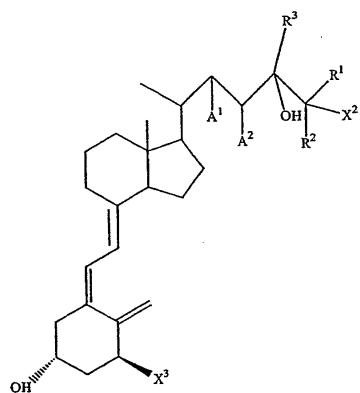
2

D

IV 24-

D

IV



IV ,

A¹ A²

C-22 C-23

;

R¹ R², O- , O- , O- , O- , O- [, R¹ , R² , , C₃-C₈ ;R³
, O-X³X²

, O- , O- , O-

;

8.

2

D

1 - D₄; 1 ,25-D₂; 1 -D₂; 1 ,24-D₂; 1 ,24,25-D₄; 24-D₃; 1 ,25-D₂; 1 ,24,25-D₂;D₄

9.

3

, ARVDD

가 1

D

10.

3

, ARVDD

가 1,25-

D₃

11.

3

, ARVDD

가 1,25-

D₃

12.

2 , D

13.

12 , 가 D , , , , ,

14.

12 , D ,

15.

2 , D가 (episodic)

16.15 , D 10 μ g 300 μ g**17.**

16 , D 1 , 25- D 3 1 - D 3

18.

15 , 1 12 1

19.

2 , D

20.

19 , D

21.

20 , D

22.

19 , D

23.20 , D 1 μ g 300 μ g**24.**23 , D 20 μ g 100 μ g**25.**

19 , D

26.

20 , D , ,

27.

D (ARVDD) D

35 , D

37. $1,25\text{-}(\text{OH})_2\text{D}_3$, $1,25\text{-}(\text{OH})_2\text{D}_3$.

38. / D (ARVDD), D

39. (i) D 가 D / 가 D (ARVDD) (ii)