



MM

MM

가

[Laktinen

, Lancet 1992, 340, 1049-1052; McCloskey , B.J.Haematol., 1998, 100, 317-325; Berenson , N.Eng J.Med. 1996. Vol. 334, No.8, 488-493].

가

[Hortobagyi G.N. , 가

(Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases), Protocol 19 Aredia Breast Cancer Study Group, New England Journal of Medicine, 1996; 335: 1785-91; Kanis J.A. .

(Clodronate decreases the frequency of skeletal metastases in women with breast cancer, Bone, 1996; 19: 663-7)].

(osteoblastic) ( )

가

(

) 가

[Silvio Adami, Cancer 1997

; 80:1674-79].

가

[Boissier , Cancer Res; 57: 3890-3894; 1997],

[Brown , (Effects of Zoledronate on Prostate Cancer Cells), ASBMR 2000; Lee , 가 . Cancer Research, 2000/2001];

[Corey , (Effects of Zoledronic Acid on Prostate Cancer in Vitro and in Vivo), Amer.Assoc.Cancer Res. 2000 10 ].

가

ZOMETA) (R) ,

(Novartis Pharma))

N-

가

N-

N-

( , )

가

( ) ,

N-

(i) N- ;

(ii) N- , 가

;

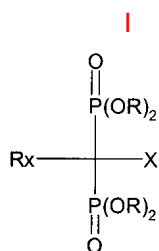
(iii) N-  
N-  
, N- (SREs)  
(SREs)

(i) SREs N- ;

(ii) N-  
SREs  
(iii) SREs N-

, , , ,  
SREs  
가

, N- I 가



X , , , C<sub>1</sub>-C<sub>4</sub> ;

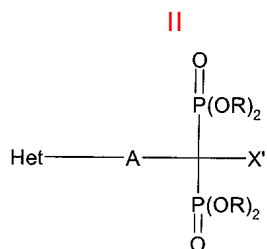
R C<sub>1</sub>-C<sub>4</sub> ;

Rx ( - )

가 , : 3- -1- -1,1- ( ), (A  
PD); 3-(N,N- )-1- -1,1- -APD; 4- -1-  
-1,1- ( ), ; 1- -3-( )-  
; 6- -1- -1,1-  
-BP; 3-(N- -N-n- )-1- -1,1- -APD (=BM 21.0  
955); 1- -2-( -1- ) -1,1- ; 1- -2-(3- )  
-1,1- ( ), N- N-  
NE-10244 NE-10446; 3-[N-(2- )-N- ]-1- -1,1  
; 1- -3-( -1- ) -1,1- EB 1053 ( (Leo)); 1-(N-  
) -1,1- FR 78844 ( (Fujisawa)); 5- -3,4-  
-2H- -3,3- U-81581 ( (Upjohn)); 1- -2-(

[1,2-a] -3- ) -1,1- , YM529 .

가 , N- II



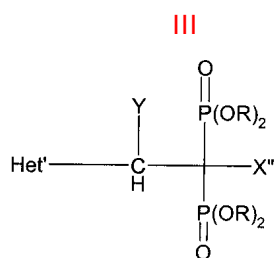
Het , , , , , , , 1,2,3- , 1,2,4- ;

A 1 8 , ;

X' , ;

R .

가 , III



Het' , , , , , , 5- , , , C<sub>1</sub>-C<sub>4</sub> , C<sub>1</sub>-C<sub>4</sub> , Het' 2 ;

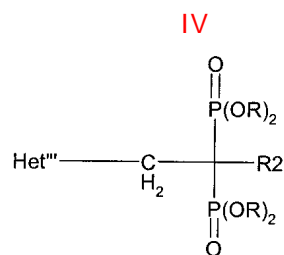
Y C<sub>1</sub>-C<sub>4</sub> ;

X' , , , C<sub>1</sub>-C<sub>4</sub> ;

R C<sub>1</sub>-C<sub>4</sub> .

IV

, 가 .



Het'' , 2H-1,2,3-, 1H-1,2,4 4H-1,2,4- , , , ( , , / / C- - , 가 N- ( , , / - - ) - N- ; R2 , , , , 7 가 .

N-

2-(1- -2- )-1- -1,1- ;

2-(1- -2- )-1- -1,1- ;

2-(1- -4- )-1- -1,1- ;

1- -2-(1- -4- ) -1,1- ;

1- -2-(1- -4- ) -1,1- ;

2-(1- -2- ) -1,1- ;

2-(1- -2- ) -1,1- ;

2-( -1- )-1- -1,1- ;

2-( -1- ) -1,1- ;

2-(4H-1,2,4- -4- )-1- -1,1- ;

2-( -2- ) -1,1- ;

2-( -2- ) -1,1- ;

2-(2- -4(5)- ) -1,1- ;

2-(2- -4(5)- ) -1,1- ;

2-(4,5- -1- )-1- -1,1- ,

2-(2- -4(5)- )-1- -1,1- 가 .

( ) 가 N- 2-( -1- )-1- -1,1- 가 , , la, lb, IIa IIb , .

가 , 1, 2, 3 4 , 1 2 가 , , .

가 가 , .

가 , .

N- EP-A-513760, 13-48 ). , 3- -1- -1,1- ( 3,962,432 , 1- -2-( -1- ) -1,1- 4,639,338 4,711,880 4,939,130 , 4,777,163 4,687,767 .

N- , / , - .

, N- , .

N- 가 , , .

, , ( , ) , .

, ( , ) , N- , , 가 .

, N- , 가 .

N- , / , , .

, 0.002 20.0 mg/kg, 0.01 10.0mg/kg 1 75kg .

'mg/kg' - - kg mg .

, - 1 ( ) - 1 1 , 1 1 .

, , N- MM .

, - MM



가 가 . , , , ,

N-

\_\_\_\_\_1 : :  
:

( ) 197.3mg

52.7mg

( (R) PH 105)

250.0mg

:

HP-M 603 10.0mg

2.0mg

8.0mg

270.0mg

- :

(Eudragit) (R) L30D ( ) 90.0mg

21.0mg

(Antifoam) (R) AF 2.0mg

7.0mg

390.0mg

, (R) PH105 , , ,  
, (R) L30D, HP-M 603, (R) AF (PEG) 8000 -  
(Hofliger and Krag) ( 0) , ,

\_\_\_\_\_2 : 1- -2-( -1- )- -1,1-

\_\_\_\_\_:



(PIB)300 ( (Oppanol)B1, BASF) 5.0g

PIB 35000 ( B10, BASF) 3.0g

PIB 1200000 ( B100, BASF) 9.0g

( (Escorez) 5320, ) 43.0g

1- -2- 20.0g

( (Azone), , (Irvine)/CA)

20.0g

100.0g

\_\_\_\_\_ :

300mm , 150g 100-125  
(75 g/m<sup>2</sup> (60 15 ) (Hostaphan), (Kalle))  
( 75mm, (Laufenberg)) 5 30cm<sup>2</sup>

\_\_\_\_\_3: 1.0mg , 1- -2-( -1- ) -1,1- ( )  
. 1ml , ( 1mg/ml) .

\_\_\_\_\_ :

( ) 1.0mg

46.0mg

3 ×2H<sub>2</sub>O 3.0mg

1ml

1ml

1ml , 3 ×2H<sub>2</sub>O pH 6.0 . , 가 ,  
, .

\_\_\_\_\_4 : , 2 5 .  
( 3mg/ml) .

\_\_\_\_\_ :

19.73mg

( 5.0mg )

250mg

5ml

\_\_\_\_\_

## 1.

SA ] , 1 가 [ , 가 P  
 (4 8mg) 가 ,  
 (SREs) , , SREs가  
 SRE 가 SRE  
 가 , , , 가  
 가 , , 가  
 가 . ,  
 가 .

## 2.

## 2.1

1 , , , , 가 , PSA (2.3.2 ) ,  
 가 PSA 3 PSA PSA PSA  
 PSA ( , PSA PSA 1 PSA PSA ),  
 2 . 가 PSA  
 ( / ) , 가 ( 2 -  
 ) 1  
 , 1 ( ) , 1 . ( 1 , 2 34  
 ) ( (50 ng/ml  
 ), 3 ( 2 ( 2 ) , 2  
 ).  
 가 3 4mg ,  
 8mg , 500mg (400 500 I.U. 1:1:1 D  
 )  
 SRE - (SRE's) SRE (4 ) .  
 , ( ) 가 ,  
 , 가 ; , -  
 가 ; 가 가 ; PSA  
 , 24  
 , 14 ( 1)  
 , 2 , 2 , 60 (20  
 ) 2 , 1 1 2 , 2 가 3  
 6 (12 ) . 2 1 ,

(가) 173 ) , 550 가 ( 519 (24  
)  
가  
가  
,  
.  
-  
,  
,  
,  
. ,  
24 6 .

* - 1 ( )																					
		가																		가 1 2	
	1	2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21																		22	
	-2	0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48 51 54 57																		60	
		3 4mg																		3 4mg	
		3 8mg																		3 8mg	
		3																		3	

- 2 ( )												
	가											가
	23	24	25	26	27	28	29	30	31	32	33	34
	63	66	69	72	75	78	81	84	87	90	93	96
	3	4mg										
	3	8mg										
	3											

$$^* \quad 2 \quad , \quad -3 \quad +7 \quad .$$

: 12

가 :

15 (60 ) 1

$$9 \quad (36) \quad 2$$

: 24 (96 )

: 36

## 2.2

## 2.2.1

- 
- 18
- 
- 
- 가 ( $>3$ ) 가 , 3 가 , 1 가
- 1 ( ) :
- 2 , 3 PSA . PSA
- 0.4ng/ml
- 1 :
- 가 1
- 0, 1 2 ECOG 가 .
- 1 ,
- ( 2 ) ( ) .
- 1 1 2 ( 1 ) .
- 가 (50ng/ml ) ( 1) .
- 2 3 ( ) .
- 
- ( 2) 2 , .
- ( 2) 30 ( ) .
- 가 , 가
- 3.0mg/dL (265  $\mu$  /L)
- 8.0mg/dL (2.00 /L) 11.6mg/dL (2.90 /L) ( )

5  
6 ( ), ,  
가 .

2.3

2.3.1

24 3 5-  
500mg  
(open-label)  
가 '1  
'1  
가  
( )

4mg (4000µg)  
8 , 36 46 (2 8 )  
가 5 4mg  
5ml  
(0.9%) 가 50ml가 ( 2 33),

- 3 50ml 4mg + ( ) 500mg  
1
- 3 50ml 8mg + ( ) 500mg  
1
- 3 50ml + ( ) 500mg 1

3- ,

		#		가	
4mg, 3 NS I.V.	2-33	4.0mg/ 5ml/ 1	5.0ml	45ml	50ml
8mg, 3 NS I.V.	2-33	4.0mg/ 5ml/ 2	10ml	40ml	50ml
, 3 NS I.V.	2-33	N/A	N/A	50ml	50ml

가 , 5- 50ml : 8mg 가 15- 100ml  
 , 8mg 4mg . 8mg  
 , 8mg 4mg .

## 2.4

가 :

. , ,  
 . /  
 . /  
 . ( , , , ( , ,  
 ) )가 / . , ( , ,  
 - )가 - 가 (2.3.3 ).  
 . - / / .  
 .

## 3.

(N=208) 44.2% , 4mg (N=214) 8/4mg (N=221) 33.2% 38.5%  
 - (p=0.021 0.222 ). 4mg 8/4mg  
 13.1% 14.9%  
 (p=0.015 p=0.054 ). 4mg  
 , 8/4mg 363 320 (p=0.011 0.491 ). 15-  
 4mg

3 4mg 15- , 가  
 - .

(57)

1. N- , 가  
 .

2. N- .

3. N- .

4. N-  
 .

5.

N- , 가

6.

가 N-

7.

SREs N- ,

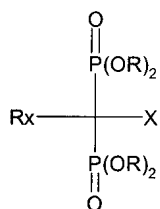
8.

SREs N-

9.

1 2 , N- 가 I 가

< I>



X , , , C<sub>1</sub>-C<sub>4</sub> ;

R C<sub>1</sub>-C<sub>4</sub> ;

Rx ( - )

10.

9 , N- 가 :

3- -1- -1,1- ( ), (APD);

3-(N,N- )-1- -1,1- , -APD;

4- -1- -1,1- ( ), ;

1- -3-( )- - , , ;

6- -1- -1,1- , -BP;

3-(N- -N-n- )-1- -1,1- , -APD (=BM 21.0955);

1- -2-( -1- ) -1,1- , ;

1- -2-(3- ) -1,1- ( ), N- , N-10244 NE-10446;

3-[N-(2- )-N- ]-1- -1,1- ;  
 1- -3-( -1- ) -1,1- , EB 1053 ( );  
 1-(N- ) -1,1- , FR 78844 ( );  
 5- -3,4- -2H- -3,3- , U-81581 ( );  
 1- -2-( [1,2-a] -3- ) -1,1- , YM529,  
 가 .

# 11.

<sup>1</sup> 2 ( , N- 가 2-( -1- )-1-  
 -1,1- ( ) 가 .

# 12.

N- - - ,  
 .