

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

(51) . Int. Cl.7 (11) 10-2004-0053291  
A61K 38/21 (43) 2004 06 23

(30) 60/337,948 2001 11 09 (US)

(71) 94608 2000 1640

(72) 94563 55

95030 17610

94526 1940

(74)

(54) 가

, , , , 가 (IFN)  
,

(1) 가 IFN 기

(2) - 가 IFN 가 IFN

가 , , , ,

가

, ,  
ensus) 가 . . , ( , ) (cons  
C , C  
,

, , ( ) ,  
, , , , ,  
가 . . , , , ,  
가 . . , , , ,  
,

가 , , , ,  
가 , , , ,  
, C , , , ,  
,

: (~ 10-15%); , C  
(~ 20-25%); (~ 30-40%). (~ 30-40%); (~ 10-15%); (pegylated)  
,

(1) 가 , , , ,  
(2) . , , ,  
1 2 , , ,  
( , ) , , ,  
,

, , , ,  
가 가 , , ,  
,

( -2c FDA (labelling) );

가 . . . . . 가

가 (IFN)

(1) , (2) - 가 가 IFN

, , 가 , 가 , 가

가 (IFN) . , , , ,

1: , 가 1 C (HCV)  
(RNA)

(highly homologous) ( , ) , Intron-A (Schering Corporation, Kenilworth, NJ) -2b, Roferon (Hoffmann-La Roche, Nutley, NJ)  
-2a, Berofor 2 (Boehringer Ingelheim Pharmaceutical Inc., Ridgefield, Conn)  
-2C, Sumiferon (Sumitomo, ) , Wellfe  
ron -n1 [INS; Glaxo-Wellcome Ltd., London, ], [U.S. Pat. Nos. 4,897,471 4,  
695,623] (Amgen, Inc., Newbury Park, Calif.) Interfero  
n Sciences Alferon (Purdue Frederick Co., Norwalk, Conn.)  
-n3

가 ( ), [U.S. Pat. N]  
os. 5,120,832 5,231,176]  
가  
가 ( 65%), ( 35%),  
가  
가  
가  
가

, IFN

가 IFN ( $\mu$ g)	1	3 (factor)	가 IFN ( $\mu$ g)	2	가 IFN (disorder)
가 (MIU)	1	135-700 $\mu$ g	가 IFN	27-420	

(current edition)

(non-Hodgkin's lymphoma),

T-

(Kaposi's sarcoma),

가

IFN, IFN, IFN, IFN, IFN, IFN, -

가

가

가

IFN,

IFN,

IFN,

IFN,

IFN,

'1

가

)

('2

)

2

가

(MTD)

MTD 가

가

).

[ 1]

C			
#			MTD
1	-2a	C	6 MIU TIW sc (FDA Summary Basis of Approval (PLA 94-0782, 29 Oct 1996))
2	-2b	C	3-5 MIU TIW sc (FDA)
3	PEG -2b	C	105 µg * QW sc ( ≈ 21 MIU QW sc) (FDA)
4	PEG -2c	C	180 µg QW sc ( ≈ 36 MIU QW sc)
5	-2a		30 MIU/wk (+ Roth et al. Acta Oncol 1999;38(5):613-7)
6	-2a		7 Rajkumar SV et al Int J Radiat Oncol Biol Phys 1998 Jan 15;40(2):297-302 15.5 MIU/wk
7	-2a		6 MIU TIW sc ( Hubel K et al. Leukemia 1997 Dec;11 Suppl 5:547-51)
8	-2a		5 MIU TIW sc ( Adamson PC et al. J Clin Oncol 1997 Nov;15(11):3330- )
9	-2a		3 MIU QD×7d×4 wks ( Gause BL et al. J Clin Oncol 1996 Aug;14(8):2234-41 +IL2)

10	-2a		3.4 MIU TIW (5-FU+ )	Trudeau M et al. Cancer Chemother Pharmacol 1995;35(6):496-500
11	-2a		3.4 MIU QD×5d 4 +RT, + , + 1 ( )	Vokes EE et al. Cancer Chemother Pharmacol 1995;35(4):304-12
12	-2a		3 MIU TIW (+ )	Gosland MP et al. Cancer Chemother Pharmacol 1995;37(1-2):39-46
13	-2b		3.6 MIU QD sc	Dorr RT et al J Interferon Res 1988;8:717-25
14	-2b		24 MIU/m <sup>2</sup> QD iv 7 ; 2 12 MIU/m <sup>2</sup> QD (1 )	Iacobelli S et al Am J Clin Oncol 1995;18:27-33
15	-2b		5 MIU/m <sup>2</sup> TIW sc	Kirkwood JM et al J Clin Oncol 1996;14:7-17
16	PEG -2b		7.5 µg/kg QW (35 MIU/wk)	Talpaz M et al, Blood 2001;98:1708-13
17	C		3-9 µg ** TIW sc ( ≈ 3-9 MIU TIW sc)	FDA ( <a href="http://www.fda.gov/cber/sba/ifnam/g100697S.pdf">http://www.fda.gov/cber/sba/ifnam/g100697S.pdf</a> )

b : \* IFN 5 µg ; \*\* -2a -2  
 , , , MIU  
 1 MIU 10<sup>6</sup> , µg -  
 , ( , ), ( , )  
 , MIU 가 , . MIU 가  
 , MTD 가 , .

[ 2]

#			4 (MIU)
1	-2a	C	72
2	-2b	C	60
3	PEG -2b	C	34 84 *
4	PEG -2a	C	36 144 *
5	-2a		120
6	-2a		62
7	-2a		72
8	-2a		20
9	-2a		84

10	- 2a		41
11	- 2a		68
12	- 2a		36
13	- 2b		100
14	- 2b		290
15	- 2b		60
16	PEG - 2b		140
17		C	36-108

\* , MIU/ $\mu$ g

FDA MTD I, II / III

(phase) I MTD 가 3-6 27  
 450  $\mu$ g 1 - 2a [Motzer RJ et al J Clin Oncol 2001;19:13  
 12-9 ]. , 7 % 가 , 450  $\mu$ g - 2a - 2a  
 oconjug Chem 2001;12:195-202 ]. 가 , [ Bailon p et al Bi  
 180  $\mu$ g [PEGINTERFERON ALFA-2a IN PATIENTS WITH CHRONIC HEPATITIS C S. Zeuzem S, Feinman SV, Rasenack J et al. New Engl J Med 2000;343:1666-72].

, 2 MIU 가 4  
 180 MIU , , MIU , 가 , 가  
 . - 2a, - 2b,  $\mu$ g MIU , ,  
 , , MIU/ $\mu$ g , , MIU/ $\mu$ g  
 , 가 ( 3 )  $\pm$  SU MIU

[ 3 ]

4				(MIU/ $\mu$ g )	(MIU) $\pm$ SD
1	1 - 4	MIU/ $\mu$ g	- 2a	- 2b,	90 $\pm$ 37
		3 MIU $\approx$ 15 $\mu$ g			
2	1 - 4	40 %, $\mu$ g	$\approx$ $\mu$ g		51 $\pm$ 19
3	1 - 4, 17	1 - 2b	$\approx$ 5x	- 2a	108 $\pm$ 52
4	1 - 4, 17	2	$\approx$ 1 MIU/ $\mu$ g		48 $\pm$ 17
5	5 - 16	3 MIU $\approx$ 15 $\mu$ g			94 $\pm$ 33
6					





가 , , , ,

가

( )

19 420MIU/  
).  
, QD, QOD, TIW QW 15 100μg/  
1, 270 10,000μg (depot)  
1  
, 2 1  
) 12 , 175μg/  
2100μg 가 IFN 35 105 MIU/  
(12 × 175),  
24 4200μg (24 × 175) 가

C

, 가 ,  
가

가

, 가 ( , , , , ) 가 , 가  
가 , ( 가 .  
( )

DUROS® (ALZA Corporation)

DUROS ®

( ) 가 , ( ) , , , , , , , , ( )





, Tylenol®, Benadryl®, 가

, , ,  
, 가

RNA (HCV RNA) 가

- (a) 가 ALT
  - (b) 가 AST
  - (c) 가
  - (d) HBsAg, -HBc , -HBe
  - (e) (stigmata)
  - (f) ,
  - (g)

- 2

- (a)
  - (b)
  - (c) (mass)
  - (d)

- 2

- (a)  
(b)  
(c)



가  
1 HCV RNA . 1 - 5  
5). , 1 . 45, 60 90 µg TIW (135, 180, 270 µg/1 ) , 12 ( .  
80% 1 (HCV RNA ) 2  
2, 3 4 ALT  
1  
( 6).

## [ 5]

HCV RNA		
(µg/1 )	(MIU/ )	(%)
45	18	20
90	36	20
135	54	60
180	72	82
270	108	100

2, 3 4 1 100% 270 µg/1

## [ 6]

ALT (%)		
(µg/1 )	ALT	(%)
45	50	
90	50	
135	60	
180	57	
270	100	

(genotype) 2, 3, 4 ( , 100 % 270 µg/  
(week) ).

가 가 ( 7). 1 가

## [ 7]

	(%)				
	45 µg	90 µg	135 µg	180 µg	270 µg
	33	63	67	80	100
	53	63	42	27	50

	67	13	33	40	0
	47	25	8	13	0
	53	13	0	13	0
가	33	13	17	13	0
	40	0	0	13	0
	33	0	8	0	17
	20	13	17	20	0
	27	13	17	7	0
	7	25	17	0	17
	20	0	0	13	0
	13	13	0	13	0
	20	0	0	13	0
	20	13	0	7	0
	0	13	0	27	0

가 , C  
 가 . Peg + (oral ribavirin)  
 가 , peg +  
 가 , peg +

가 peg  
 ( 8).

[ 8]

	(6 MIU TIW)		180 µg/ )		(		+	
	VR(%)	BR(%)	VR(%)	BR(%)	VR(%)	BR(%)	VR(%)	BR(%)
Zeuzem S	28	39	69	46	-	-	-	-
Heathcote EJ	12	19	38	34	-	-	-	-
McHutchison JG	-	-	-	-	29	24	53	58

VR = ; BR = ; '-' =

- 1. Zeuzem S, New Engl J Med 2000;343:1666-72... a study of non-cirrhotic patients with chronic hepatitis C
- 2. Heathcote EJ, New Engl J Med 2000;343:1673-80... a study of cirrhotic patients with chronic hepatitis C
- 3. McHutchison J, New Engl J Med 1998;339:1485-92... a study of non-cirrhotic patients with chronic hepat

it is C.

2

가 ) -  
17/D (YFV) 3 6 가  
, , ( ), ( )  
CPE 가  
CPE Cell Titer 96® AQueous One Solution Cell Proliferation assay 37  
TS [(3-(4,5-  
, PMS [ -2- )-5-(3-  
MTS ] )-2-(4- MTS PMS  
PH NADH (dehydrogenase) NAD

, , 8x12, 96- 9A 9B  
96- 1/2 . PCT 가 12 . 8  
가 9A 9B . . . . .

Media =

## Cell control =

Virus control =

Conc =

[ 9A ]

	1	2	3	4	5	6
1	Media	Media	Media	Media	Media	Media
2	Cells + Drug 1	Cell Control	Cell + Virus + Drug 1			Cells + Drug 1

	conc 1		conc 1, 3		conc 1
3	Cells + Drug 1 conc 2	Cell Control	Cell + Virus + Drug 1 conc 2, 3		Cells + Drug 1 conc 2
4	Cells + Drug 1 conc 3	Cell Control	Cell + Virus + Drug 1 conc 3, 3		Cells + Drug 1 conc 3
5	Cells + Drug 1 conc 4	Virus Control	Cell + Virus + Drug 1 conc 4, 3		Cells + Drug 1 conc 4
6	Cells + Drug 1 conc 5	Virus Control	Cell + Virus + Drug 1 conc 5, 3		Cells + Drug 1 conc 5
7	Cells + Drug 1 conc 6	Virus Control	Cell + Virus + Drug 1 conc 6, 3		Cells + Drug 1 conc 6
8	Drug 1 conc 6 + Media	Drug 1 conc 5 + Media	Drug 1 conc 4 + Media	Drug 1 conc 3 + Media	Drug 1 conc 2 + Media

[ 9B]

	7	8	9	10	11	12
1	Blank	Blank	Blank	Blank	Blank	Blank
2	Cells + Drug 2 conc 1	Cell + Virus + Drug 2 conc 1, 3			Cell Control	Cells + Drug 1 conc 1
3	Cells + Drug 2 conc 2	Cell + Virus + Drug 2 conc 2, 3			Cell Control	Cells + Drug 1 conc 2
4	Cells + Drug 2 conc 3	Cell + Virus + Drug 2 conc 3, 3			Cell Control	Cells + Drug 1 conc 3
5	Cells + Drug 2 conc 4	Cell + Virus + Drug 2 conc 4, 3			Virus Control	Cells + Drug 1 conc 4
6	Cells + Drug 2 conc 5	Cell + Virus + Drug 2 conc 5, 3			Virus Control	Cells + Drug 1 conc 5
7	Cells + Drug 2 conc 6	Cell + Virus + Drug 2 conc 6, 3			Virus Control	Cells + Drug 1 conc 6
8	Drug 2 conc 6	Drug 2 conc 5	Drug 2 conc 4	Drug 2 conc 3	Drug 2 conc 2	Drug 2 conc 1

+ Media + Media + Media + Media + Media + Media

CPE  
(IC50)  
(semilog)  
50/IC50  
.

50%  
.

CPE  
(TC50)  
(TI50)  
TC

( -2b) 가 ( 10).

[ 10 ]

	IC50(IU/mL)	TC50(IU/mL)	TI(TC50/IC50)
-2b		> 200	NA
가	0.8	> 5000	> 6300

. . . . . 가 . . . . .  
200 IU/mL - 2b -  
6300 TI50 가 . . . . .

(57)

1

가 (IFN)  
가(non-omega) IFN

2. 1 , 가 IFN (μg) 가 - 가 IFN (μg)  
     1     3 (factor)

3. 2 , 가 IFN  $\mu$ g IFN  $\mu$ g 2 .

4. 2 가 IFN 135-700  $\mu$ g/, 가 IFN 27-420 (million IU)

5

1 ,

6.

5 ,

7.

6 , B, C, D, G

8.

1 ,

9.

5 ,

10.

1 , - 가 IFN 1 2

11.

1 , 가 IFN

12.

11 , , , , , C , -2, , -2

13.

12 ,

14.

13 , , , , , 1 400 1  
,200mg

15.

12 , , , , , , VX-148, VX-497 VX-944 ,

16.

15 , , 1 200 4,800mg

17.

1 , 가 , (enterally),

18.

17 , 가

19.

18 , 가

20.

19 , 가

21.

17 , 가

**22.**

21 , 가 .

**23.**

21 , 가 .

**24.**

21 , 가 - (non-gel)

**25.**

19 , 가 3 .

**26.**

1 , .

**27.**

26 , , , , , , , , , , , , , , , , , , ,  
 n-Hodgkin's lymphoma), T- , , , , , , , , , , , ,  
 ,  
 (Kaposi's sarcoma), -

**28.**

26 , , , , , , , , , , , , , , , , , , ,

**29.**1 , , , , , , , , , , , , , , , , , , ,  
 - IFN, IFN 1 , , , , , , , , , , , , , , , , ,**30.**

1 , , , IFN, IFN, IFN, IFN, IFN, - IFN, IFN  
 2 C , , , , , , , , , , , , , , , , , , ,

**31.**

1 , , , , , , , , , , , , , , , , , , ,  
 (marker) , , , , , , , , , , , , , , , , , ,

**32.**

31 , B, C, D .

**33.**

31 , .

**34.**

31 , .

**35.**

31 , 가 .

**36.**

31 , .

**37.**36 ,  
 T- ,



51

가 1

53.

51

가 IFN

54.

51

가 IFN

55.

가  
가 IFN

가 (IFN)

1

유전자형1을 갖는 환자에서의 평균 HCV RNA 수준

