

2002 - 0071032  
2002 09 11

WO 2001/58447  
2001 08 16

1

(54)

; ;  
 8 가 . ,  
 8  
 (Merck Manual, 16th Ed., 1992).  
 가 (nausea), (vomiting), (pruritus), (urinary retention) (respiratory depression)  
 (Gan , Anesthesiology , vol. 87, No.5, 1075 - 1081, (1997)).  
 가 가 (S  
 hen , Brain Res., Vol.597, 74 - 83(1992)).  
 , Gan (naloxone, ) 0.25 $\mu$ g  
 $\cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  1 $\mu$ g  $\cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  가 ( ,  
 ) (Anesthesiology, vol.87, No.5, 1075 - 1081(1997)).

가 .

가

(intranasal) , 가 , (oral mucosal)

(hyperexcitability), /

가

5,512,578 , 5,472,943 , 5,580,876 5,767,125 (Crain )

가

가

가

(controlled - release dosage form)"

( ) ( )가 ( " MEAC" )

( ) 가

Crain

( ,

37 (pH 1.6 7.2) 900Mℓ 100rpm U

SP Paddle Method(U.S.Pharmacopeia XXII(1990))

8 가 ( ,

가 ). , ( 12 ), 1 - 1 ( 24 )  
3  
/ 5 , 7 ,

( ) ,  
.

가 , 가  
가 - , , / ,

가

( )가 가  
/ - , , ,

가

( - ) 100 1000  
. Crain ,  
 , , .

가, 가 가 ( ) 가  
( 10 100 )  
가 - ,

10 100

가

가

가 가 ( ),  
가

/

15mg

1

[ 1 ]

|  |       |
|--|-------|
|  | (mg)  |
|  | 13.5  |
|  | 90.0  |
|  | 15.0  |
|  | 3.375 |
|  | 1.8   |
|  | 135.0 |
|  | 9.0   |
|  | 27.0  |

(bimodally action opioid agonists)"  
 opioid receptor)  
 (nociceptive neuron)  
 (inhibitory and excitatory o  
 (opioid agonist)"  
 (opioid antagonist)"  
 (stereoisomer),  
 (enantiomer),  
 (diastreomer),  
 (tautomer)  
 (asymmetric center)  
 E Z  
 , N,N' -  
 , p -

, " " 가 ( )

" (chiral center)"

" (eantiomer)" " "

" "

" (resolution)" 가

, 가

(Transdermal delivery system)

가

( ) , 48 72 (2 3 ) , Duragesic ( )

( )

( ) ,

가

50 100

(Wallenstein SL , Crossover Trials in Clinical Analgesic Assays; Studied of Buprenorphin and Morphine , Pharmacotherapy, G(5): 225 - 235, 1986).

5,069,909(Sharma )

가

4,806,341 (Chien )



( )

5,026,556 (Drust ) ,  
 3 4 , 3 6 ,  
 ;  
 : 60:40 99:1  
 4,588,580 (Gale ) 5 100cm<sup>2</sup>  
 가 가 0.1 50 %  
 47 95%, 1 10%, 0.1 10%,

가  
 ,  
 - - , ,  
 , /

/ , 1 , 0 , 1 0  
 , " 1 " 가  
 . " 0 " 30% 48

" (delivers)" 가  
 " "  
 g /cm<sup>2</sup>/hr , 72 1.2mg  
 가 16.67g/hr  
 ,  
 " (flux rate)"

5,968,547  
 ; 72 3 8  
 6g/hr ; 72 120 0.3 9g/hr

가

20 90 % , 0.1 30 % , 0.1

20 % 0.1 30 %

0 150% A:B ( , A B 8 85g/mm, : (1) 0.5 4.9 $\mu$ m, 3

B )가 1.0:5.0 , A , A

0.001 3.0 $\mu$ m, (b) 0.01 1.0 % , (a) 1.

5 ;

(2)(a) 2 60 $\mu$ m , (a)

; (b) : (a)

; 2 25

% 1 12 %

, 10 100cm<sup>2</sup> 1 100 $\mu$ g/hr .

: (a)

; (b) 가

,

: (a) 3 4 , 3 6 ,

; (b) , , 60:40

99:1 .

(Oral mucosal delivery system)

, /

MxQuinn, R.L. ( Sustained Oral Mucosal Delivery in H

uman Volunteers J.Controlled Release ; (34 1995(240 - 250)).

8%, Carbopol 934 52%, 35% 5% 2 -

( )

(0.5cm<sup>2</sup>) 0.6mm

2.9mg 12 .

( 25pg/M $\ell$ ) ,

가 가 가 ,

24 . 0.42  $\pm$  0.18mg

가

Carbopol 934,

(Suppositories)

( )

5,215,758

( )

pH,

pH, p

Ka,

/

가

12

18

가

가 - , -

Novata TM(AB, AB, B, BC, BD, BBC,

E, BCF, C, D 299 ) Witepsol TM(H5, H12, H15, H175, H185, H19, H32, H35, H39, H42, W25, W31, W35, W45, S55, S58, E75, E76 E85 ) 12 18

( , ),

20

90

%

65

80

%

가

가

가

가

(Compositions for intranasal administraion)

205

282 PCT WO8203768( ), 5,629,011 ( - 6 -  
 - 6 - 가 )  
 가

가 ( 가 )가

( Modified Starches: Properties and Uses, O.B. Wurzburg, CRC Press Bo  
 ca Raton(1986)).

(DEAE - ),

( Davis , " Microspheres and Drug Ther  
 apy" , Elsevier Biomedical Press, 1984).

가

G

B 1 518 121 EP 223 303

(coacervation)

( Florence and Attwood, Physicochemical Principles of Pharmacy 2en E d., MacMillan Press, 1988, Chapter 8).

( Fisons Lomudal System).

. 가  
( Bell. A. Intranasal Delivery Devices, in Drug Delivery Devices Fundamentals and Applications, Tyle P.(ed), Dekker, New York, 1988).

가

가 (Injectable formulations)

가 5,942,241 (Chasin )

가

가

가

/

가 20 120 5 200

가 가

가 . 1 50%

2 , 6 50% 가

2 2 100% 1 3 가

1 , 0 , - - , 가

/

(

- CO - ), 가 , 가 , - 1,4 -

- 1,4 - 가 (HES),

=4:1 , 80 % , 20 % 1% ),

1 가

4,293,539

가 ( Dowex HCR - W2 - H ).

0.01 20

100 2502

가 , 2%

가  
WO 95/13799  
1, 2  
1, 2  
1, 2

(Wurster air suspension coating apparatus)

(Controlled release oral dosage forms)

" (release rate)"

100rpm) , U.S.P. Paddle(

100:1 . , 40:1 50:1 , 20:1 . 1:1

100 100 .

가 , 가

pH - pH - pH -

8 , 12 24 가 pH -

pH - 가

pH - 가

(CAP), (PVAP),

(i) ; (ii) ; (iii)

2 25 %  
5,273,760 5,286,493

5,324,351 , 5,356,467

5,472,712

(Alkylcellulose Polymers)

가 Aquacoat (FMC Corp., , )

Aquacoat 가 Aquacoat 가



Surelase (Colorcon, Inc., , , )  
가 가 , 가 (

, ( )

(Acrylic polymers)

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

NF XVII 4

4 가  
가 .

pH - .

nc) Eudragit Eudragit E  
Eudragit S pH 6.5 Eudragit L pH 5.7 pH 6  
pH 7 , Eudragit RL Eudragit RS  
pH , Eudragit RL RS pH -

Rhom Pharma  
Eudragit RL30D Eudragit RS30D Eudragit RL30D Eudragit RS30D  
4 가 Eudragit RL30D 1:20 , Eudragit RS30D 1:40 150,000 . RL(  
) RS( ) . Eudragit RL/RS  
가 가 .

Eudragit RL/RS

100% Eudragit RL, 50% Eudragit RL  
50% Eudragit RS 10% Eudragit RL: 90% Eudragit RS  
, Eudragit L .

가 가 , ,  
가 가 ,

가 .

50 % 가  
가

가 ( , , , )가 가 가 , , , 가 . 가 . NF XV , , 가 1,2 - 가 , , , 가 . 가 .

nu pariel 18/20 가

가 , 가 , 가 , 가 , 가

20 ) / 가 ( nu pariel 18/ 가 , , ( , Opadyry , Colorcon, Inc. ) 가 (barrier agent) .

가 . Aquacoat Surelease - Eudragi , Surelease 가 가 . t -

( , )  
가

가

가 가 Aquacoat

가

가 . 가

, 가

Opadry

가

가

3,845,70 , 3,916,889 , 4,063,064 4,088,864

가

pH

pH -

가

/

가

( 8 50, 12 40)

Eudragit RSPO -

가

1 80 %

25 90

가 60 % 60  
%

30 200 / 45 90  
 30 200 , 45 90  
 30 200 , 45 90

30 100  
 30 100

40) 가 ( 8 50, 12  
 25 90  
 60 %

가  
 12 36,  
 14 22  
 ( 1 6)

20 50 %

20 50 %

/

/ 1:3 1:4 가 1:2 1:4 ,

1,000 15,000, 1,500 12,000

( ), 12 36

2

(a)  
; (b)

12 36

; (c)

1.5 5 , 1.75 3.5

가

가

Avicel PH 101(FMC )

가 가 ( )

(a)

; (b)

가

4,861,598

[illegible]

Handbook of Pharmaceutical Excipients(American Pharmaceutical Association(1986))

Remington's Pharmaceutical Science (Arthur Osol, 1553  
- 1593(1980))

4,957,681 (Klimesche )

2 30 %

가

가

가

가

/

1

2

1

2

1 2

가

가 (Additional Drugs)

가

가

( " NSAIDS" ),

; N - - D - (NMDA)

- II (" COX - II "); /

NSAID COX - 2 가

N - - D - (NMDA) , , d - , " NMDA " NMDA - , GM<sub>1</sub> GT<sub>1b</sub> , N - (6 - ) - 5 - - 1 - 5,321,012 5, 556,838 ( Mayer ) , 5,502,058 가 / 가 . NMDA Mayer가

5,514,680 (Weber)

COX - 2

COX - 2                      5,616,601       ,    5,604,260       ,    5,593,994       ,    5,550,142       ,    5,536,752       ,    5,521,213       ,    5,475,995       ,    5,639,780       ,    5,604,253       ,    5,552,422       ,    5,510,368       ,    5,436,265       ,    5,409,994                  5,130,311    COX - 2    (SC - 58635), DUP - 697,                      (CGP - 28238),                      , 6 -                      - 2                      (6 - MNA), MK - 966(Vioxx                      ),                      (6 - MNA                      ),                      , NS - 398, SC - 5766, SC - 58215, T - 614

COX - 2

0.005                  140mg/kg                      .                      , COX - 2                      0.25mg

7g                      .

가  
(antitussive), (expectorant), (decongestant),



4 , 325 650mg , 24 가 4g / .  
1000mg .

4  
가 , ( 325 650mg 8 )

가  
가 , / ,  
325mg 15mg, 325mg 30  
325mg 60mg . 300  
7.5mg, 300mg 15mg, 300mg  
30g, 300mg 60mg .

/ 5mg( )  
500mg 가 . / 500mg 500mg  
500mg 2.5mg, 500mg 5mg,  
7.5mg, 7.5mg 650 750mg,  
10m 500, 650, 660mg 가 .  
/ ( ) 5mg 500mg 가  
5mg 325mg

가  
가 / / ,  
가 , , ,  
.  
( ) ( ) ( )  
(antitussive), (expectorant), 가 (decongestant), , ,  
.

1: /

( )

( )

/

(NXCR)

(MSCR) NXCR

[ 2]

| 1A. NXCR           |                    |        |       |
|--------------------|--------------------|--------|-------|
|                    |                    | / (mg) | / (g) |
| 1. (Drug layering) | HCl                | 2.0    | 14.0  |
|                    | nu pariel (30/35 ) | 96.0   | 672.0 |
|                    | C30                | 1.0    | 7.0   |
|                    |                    | 1.0    | 7.0   |
|                    |                    |        | 280   |
| 2. (seal coat)     | Opady Clear( )     | 5.0    | 35.0  |
|                    |                    |        | 315.0 |
| 3.                 | Eudragit RS30D( )  | 13.23  | 92.61 |
|                    |                    | 3.51   | 24.57 |
|                    | Tween 80           | 0.03   | 0.21  |
|                    |                    | 13.23  | 92.61 |
|                    |                    |        | 624.0 |
| 4.                 | Opady Clear( )     | 5.0    | 35.0  |
|                    |                    |        | 315.0 |
|                    |                    | 140    | 980   |

(NXCR )

1. HCl nu pariel

. Opadry Clear

2. Opadry Clear

3. Eudragit RS30D, , Tween 80

4. Opadry Clear

6. 60 24

(Dissolution method)

1. - USP Type II(paddle), 50rpm, 37
  2. - 1, 2, 4, 12, 24, 36
  3. - pH 6.5 900Mℓ
  4. - (HPLC)
- :
- NXCR 3 .

[ 3]

|      |    |    |    |    |    |
|------|----|----|----|----|----|
| (hr) | 1  | 4  | 8  | 12 | 18 |
| (%)  | 10 | 13 | 24 | 40 | 75 |

가 24 .

[ 4]

| 1B( - MSCR ) |                    |         |        |
|--------------|--------------------|---------|--------|
|              |                    | / (mg)  | / (kg) |
| 1.           |                    | 60.0    | 45.0   |
|              |                    | 12.0    | 9.0    |
|              | Eudragit RS 30D( ) | 2.0     | 1.5    |
|              |                    | 3.5     | 2.63   |
|              | nu pariel PG 30/35 | 16.8    | 12.6   |
|              | Opadry Blue        | 4.9     | 3.68   |
|              |                    |         | 31.5   |
| 2.           | MSIR ( 1)          | 99.2    | 74.41  |
|              | Eudragit RS 30D( ) | 4.712   | 3.53   |
|              | Eudragit RL 30D( ) | 0.248   | 0.19   |
|              |                    | 0.992   | 0.74   |
|              |                    | 1.884   | 1.49   |
|              | Opadry Blue        | 5.639   | 4.23   |
|              |                    |         | q.s.   |
|              |                    | 112.675 | 159    |

(MSCR )

1. Eudragit RS30D .
2. (Rotor processor) .
3. .
4. Eudragit RS30D, RL30D, , .

5.

(Dissolution method)

1. - USP Type II (paddle), 100rpm, 37

2. - 1, 2, 4, 12, 24, 36

3. - 55 700Mℓ, 900Mℓ

4. - (HPLC)

:

MSCR 5

[ 5]

|      |   |   |    |    |    |    |    |
|------|---|---|----|----|----|----|----|
| (hr) | 1 | 2 | 4  | 8  | 12 | 18 | 24 |
| (%)  | 4 | 8 | 23 | 49 | 70 | 83 | 85 |

가 24

1C. CR/ CR

[ 6]

|    |        | / (mg)  | / (kg) |
|----|--------|---------|--------|
| 1. | CR     | 112.675 | 159    |
|    | HCl CR | 140.0   | 105    |
|    |        | 232.675 | 264    |

(MSCR/NXCR )

MSCR ( 1B) 112.675mg CR ( 1A) 140mg

2: /

HCl (HHCR) CR

2A: HCl

[ 7]

|               | / (mg) | / (gm) |
|---------------|--------|--------|
| HCl           | 2.0    | 33.3   |
| Eudragit RSPO | 70.0   | 1166.7 |
| Eudragit RLPO | 8.0    | 133.3  |
|               | 40.0   | 666.7  |
|               | 120.0  | 2000.0 |

:

1. HCl, Eudragit RSPO, Eudragit RLPO

2.

3.

4.

5.

(Dissolution method)

1. - USP Type I(Basket), 75rpm, 37

2. - 1, 2, 4, 8, 12

3. - 1 700Mℓ , 900Mℓ

4. - (HPLC)

:

HCl 8

[ 8]

| (hr) | 1    | 2    | 4    | 8    | 12   |
|------|------|------|------|------|------|
| (%)  | 13.9 | 20.3 | 27.3 | 37.6 | 45.3 |

2B( HCl )

[ 9]

|               | / (mg) | / (kg) |
|---------------|--------|--------|
| HCl           | 12.0   | 3.2    |
| Eudragit RSPO | 76.5   | 20.4   |
|               | 4.5    | 1.2    |
|               | 27.0   | 7.2    |
|               | 120.0  | 32.0   |

:

1. .
2. HCl, Eudragit RSPO, .
3. .
4. .
5. .
6. .

(Dissolution method)

1. - USP Type I (Basket), 75rpm, 37
2. - 1, 2, 4, 8, 12, 18, 24
3. - 900Ml + 3g NaCl/L
4. - (HPLC)

:

HCl 10

[ 10]

| (hr) | 1    | 2    | 4    | 8    | 12   | 18   | 24    |
|------|------|------|------|------|------|------|-------|
| (%)  | 12.6 | 23.8 | 43.2 | 69.5 | 84.7 | 96.5 | 100.8 |

2C: HCl CR/ CR

[ 11]

|     | / (mg) | / (kg) |
|-----|--------|--------|
| HCl | 120.0  | 12.0   |
| HCl | 120.0  | 12.0   |
|     | 240.0  | 24.0   |

:

1. HCl ( 2B) HCl ( 2A)

3: / ( )

( HCl) ( HCl)

( , ) ,

[ 12]

|                    | / (mg) | / (kg) |
|--------------------|--------|--------|
| HCl                | 10.00  | 11.00  |
| HCl                | 0.50   | 0.55   |
|                    | 68.75  | 75.62  |
|                    | 5.00   | 5.50   |
| Eudragit RS 30D( ) | 10.00  | 11.00  |
|                    | 2.00   | 2.20   |
|                    | 25.00  | 27.50  |
|                    | 2.50   | 2.75   |
|                    | 1.25   | 1.38   |
| Opadry White       | 5.00   | 5.50   |
|                    |        | 31.16* |
|                    | 130.00 | 143.00 |
| *                  |        |        |

:

1. - Eudragit 가 HCl 가

2. : HCl,

3. : .

4. : .

5. : , 가

6. : .

7. : .
8. : , .
9. : .
10. : Opadry , .
- 4: / ( )
- ( ) ( HCl)
- ( ) ,

[ 13]

|               | / (mg) | / (kg) |
|---------------|--------|--------|
| ( )           | 30.00  | 108.0  |
| HCl           | 0.50   | 1.8    |
|               | 69.5   | 250.2  |
|               | 10.0   | 36.0   |
|               |        | 75.9*  |
|               | 35.0   | 126.0  |
|               | 3.0    | 10.8   |
|               | 2.0    | 7.2    |
| Opadry Purple | 3.0    | 10.8   |
|               |        | 61.2*  |
|               | 153.0  | 550.8  |
| *             |        |        |

- :
1. : HCl .
2. : ,  
HCl .
3. : .
4. : .
5. : .
6. : , 가
7. : .
8. : .



9. : , .

10. : .

11. : Opadry , .

5: /

( HCl) ( )  
Eudragit .

[ 14]

|               | / (mg) | / (gm) |
|---------------|--------|--------|
| HCl           | 12.0   | 120.0  |
| Eudragit RSPO | 76.0   | 760.0  |
|               | 4.5    | 45.0   |
|               | 27.0   | 270.0  |
| HCl           | 0.5    | 5.0    |
|               |        |        |
|               | 120.0  | 1200.0 |

:

1. : .

2. : HCl, Eudragit, , HCl

3. : .

4. : .

5. : .

6. : .

7. : 120mg .

6: /

( ) ( HCl)

[ 15]

|            | / (mg) | / (gm) |
|------------|--------|--------|
|            | 30.0   | 15.0   |
| HCl        | 0.5    | 0.25   |
|            | 44.0   | 22.0   |
| ( )        | 62.0   | 31.0   |
|            | 62.0   | 31.0   |
|            | 20.0   | 10.0   |
|            | 2.0    | 1.0    |
| Opadry Red | 10.0   | 5.0    |
|            |        | 28.4*  |
|            | 230.5  | 115.25 |
| *          |        |        |

:

1. :
  2. : , HCl, ,
  3. :
  4. :
  5. :
  6. :
  7. :
  8. : Opadry .
- 7: / ( )
- ( ) ( HCl) .
- (Eudragit
- RS 30D) ,

[ 16]

|                    | / (mg) | / (kg) |
|--------------------|--------|--------|
| HCl                | 0.50   | 1.80   |
| Eudragit RS 30D( ) | 0.03   | 0.10   |
|                    | 0.01   | 0.04   |
| ( )                | 30.00  | 108.00 |
|                    | 69.46  | 250.06 |
|                    | 10.00  | 36.00  |
|                    |        | 75.90* |
|                    | 35.00  | 126.00 |
|                    | 3.00   | 10.80  |
|                    | 2.00   | 7.20   |
| Opadry Purple      | 3.00   | 10.80  |
|                    |        | 61.20* |
|                    | 153.0  | 550.8  |
| *                  |        |        |

:

1. : Eudragit 가 .
  2. - : HCl - .
  3. : HCl , , , .
  4. : .
  5. : .
  6. : .
  7. : 가 .
  8. : .
  9. : .
  10. : , .
  11. : .
  12. : Opadry .
- 8:

WO96/19975

1

, : 2 - , ( - : :

: : 37:26:26:4:1 ) 47.83 %  
 1.139g, fp 100g, 150g, 100g, 150g,  
 200g 100g 1g . 2  
 . , 80g  
 /m<sup>2</sup> 420mm  
 가 .  
 15.mu.ab  
 16cm<sup>2</sup> .  
 9  
 9 WO 96/19975 3 . 10%  
 ( 0%, ), 10%, 10%, 1  
 1 25µg/hr  
 10mg , 12.5cm<sup>2</sup>  
 30.6cm<sup>2</sup> .  
 7  
 10mg, 0.1mg .  
 10:  
 10:1 ); DC - 360 (20cps), 10 : , 10 ( ( ) 382  
 , 80 ; M, 100g 20 .  
 (Cole - Parmer Company ) 100rpm 382 80  
 , DC - 360 20 M 가 가 20 ( 가 100g )( )  
 - 가 . 가 ,  
 - (25 100 ) 가 가  
 , 0.2 3mm .  
 3 20cm<sup>2</sup> .  
 가 3M Company  
 Scotchpak 1006 , Do  
 w Corning DC - 355 .

가 . - , 100 , DC - 355 : , 6.5 ; 30 ;  
 , 30 6.5  
 Dow - Corning 100

,

5 200 .

- : 1. , 2. -  
 , 3. - , 4. .

,  $10\text{cm}^2$  .

: 1 -

- 2 - ( Azone), .

P.R. Keshary Y.W. Chien

(Drug Develop. & Ind. Pharm., 10(6) 883 - 913(1984))

11:

(5 %) 2 - , Carbopol 934(52%), (35%)  
 ( ) (0.5 $\text{cm}^2$ ) .  
 3mg , 0.6mm .

12 - 14:

17 가

[ 17]

| ( : mg)         |        |        |        |
|-----------------|--------|--------|--------|
|                 | 1      | 2      | 3      |
|                 | 30.0   | 30.0   | 30.0   |
| HCl             | 0.5    | 0.5    | 0.5    |
| ( LF )          | 327    | 409    | 450    |
|                 | 32.5   | 40.5   | 45.0   |
| - B(Novata - B) | 1410.0 | 1320.0 | 1275.0 |
|                 | 1800.0 | 1800.0 | 1800.0 |

- B (33.4 25.5 ) 12 18

-, - .

: , HCl ,

#200 .

- B 60 .

( 50 ) 가 40

(filing kettle)

38 .

, 37 ( 36 38 ) .

15 - 19:

15 - 19 , 5,629,011 .

15 , - 6 - 가

EP 223302 . 1

100 $\mu$ m . 75mg 30M $\ell$  1g

16 , 15 가

(LPG) . LPG 100mg 가

17 , 가 : - 6 - 150

mg d ) (Chitosan) 0.5% (80% , Protan Limite

5% 가 . (Sigma Chemical Corp )

18 , 17 - -

50mg/M $\ell$  가 .

19 , 16  
 . EDTA 50mg

EDTA  
 가 .

15

20: (Microspheres for injection)

20 , /  
 , 50 %  
 ( )

50 %

50:50 (D,L)  
 가 .  
 가

co -

가

가

가

5,512,578 , 5,472,943 , 5,580,876 5,767,125 (Crain , " Crain " )

가 ,

가

8

(57)

1.

8

2.

1 , .

3.

1 , 100 1000 .

4.

1 3 , .

5.

1 3 , , , , .

6.

1 3 , , .

7.

1 3 , .

8.

1 3 , 가 .

9.

1 3 , .

10.

1 3 , , , .

11.

4 , 가 , , .

12.



4 ,  
 , 가  
 , 가  
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13.

4 ,  
 , 1  
 , 1 2  
 2  
 .

14.

1 3 ,  
 , 가  
 .

15.

1 14 ,  
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16.

15 ,  
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17.

6 , 12  
 .

18.

6 , 24  
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19.

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 , 8  
 ,  
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 -

20.

19 , 100  
 1000 .



