

LHRH , , , PPI - 149, .

가
(mammography) (radiographic imaging)

가
(實質性)

가 가
가

(, Threat,B. , 60
6 %), 25 - 50 % 가 [, Thr
eat,B. (1980)Cancer45: 2550 - 2556 ; Jackson,V.P. (1993)Radiology188: 297 - 301 : van Gils,
C.H. (1995)Br. J. Radiol.68: 1133 - 1135].
가 [, Wolfe,J.N. (1976)Cancer37: 2486 - 2492 ; Kr
ook,P.M. (1978)Cancer41: 1093 - 1097 ; Threat,B. ; Andersson,I. (1981)Radiolog
y138: 59 - 62 ; Saftlas,A.F. Szklo,M. (1987)Epidemiol. Rev.9: 146 - 174 ; Warner,E. (1992)Can
cer Det. Prevent.16: 67 - 72 ; Ma,L. (1992)J. Natl. Cancer Inst.84: 781 - 785 ; Ciatto,S. Zappa,M.
(1993)Eur. J. Radiol.17: 122 - 125 ; Oza,A.M. Boyd,N.F. (1993)Epidemiol. Rev.15: 196 - 208 ; Jenks,
S. (1994)J. Natl. Cancer Inst.86: 578 - 580 ; Boyd,N.F. (1995)J. Natl. Cancer Inst.87: 670 - 675
]. 가 2 가
: (1) (2) " (ma
sking)" [, Egan,R.I. Mosteller,R.C. (1977)Cancer40: 2087 - 2090 ; Saftlas,A.F. Szklo,M.
; Oza,A.M. Boyd,N.F.].

가

[, Jackson,V.P. (1993)Radiology188: 297 - 301
; Braeuning,M.P. (1995)Breast Cancer Res. Treat.35: 31 - 38].
가 가

(LHRH)

LHRH

LHRH

LHRH

LHRH

LHRH

LHRH

(LHRH - R)
LH

LHRH

(LH)

LHRH

LHRH

(castrate state level)(

(20 - 30 pg/Mℓ)

()

(20 - 30 pg/Mℓ)

LHRH

가

" LHRH

"

LH

" LHRH

"

LHRH - R

LH

" LHRH - R

"

LHRH

: , Folkers , 5,470,947 ; Roeske , 5,843,901 ; Haviv
 5,413,990 ; Haviv 5,300,492 ; Koerber , 5,371,070 : Hoega
 r , 5,296,468 ; Janaky , 5,171,835 ; Coy , 5,003,01
 1 ; Coy 4,431,635 ; De , 4,992,421 ; Roeske 4,851,
 385 ; Nestor,Jr. , 4,801,577 ; Roeske , 4,689,396

LHRH - R

가 :

A - B - C - D - E - F - G - H - I - J

A pyro - Glu, Ac - D - Nal, Ac - D - Qal, Ac - Sar Ac - D - Pal ,

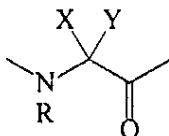
B His 4 - Cl - D - Phe ,

C Trp, D - Pal, D - Nal, L - Nal - D - Pal(N - O) D - Trp ,

D Ser ,

E N - Me - Ala, Tyr, N - Me - Tyr, Ser, Lys(iPr), 4 - Cl - Phe, His, Asn, Met, Ala, Arg Ile ;

F ;



(이때, R 및 X는 각각 H 또는 알킬이고 ;
Y는 쌍극성 부분을 포함한다.)

G Leu Trp ;

H Lys(iPr), Gln, Met Arg ,

I Pro ;

J Gly - NH₂ D - Ala - NH₂ .

, Y , , - N -
, Y , - N - .

Ac - D - Nal - 4 - Cl - Phe - D - Pal - Ser - Tyr - D - Pal(N - O) - Leu - Lys(iPr) - Pro - D - Ala - NH₂

가 :

Ac - D - Nal - 4 - Cl - D - Phe - D - Pal - Ser - Tyr - D - Pal(CH₂COO⁻) - Leu - Lys(iPr) - Pro - Ala - NH₂ ;

LHRH - R 가

A - B - C - D - E - F - G - H - I - J

, F H Q ,

A pyro - Glu, Ac - D - Nal, Ac - D - Qal, Ac - Sar Ac - D - Pal ,

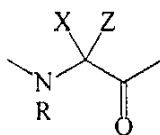
B His 4 - Cl - D - Phe ,

C Trp, D - Pal, D - Nal, L - Nal - D - Pal(N - O) D - Trp ,

D Ser ,

E N - Me - Ala, Tyr, N - Me - Tyr, Ser, Lys(iPr), 4 - Cl - Phe, His, Asn, Met, Ala, Arg Ile ;

F D - Arg, D - Lys(iPr), D - Pal(iPr), D - Cit Q , Q ;



(이때, R 및 X 는 각각 H 또는 알킬이고 ; 양이온 부분이 N-메틸 피리디늄이 아니라는 가정하에, Z 는 양이온성 피리디늄 부분 및 술포늄 부분 중에서 선택한 양이온 부분을 포함한다.)

G Lue Trp ;

H Lys(iPr), Gln, Met, Arg Q ;

I Pro ;

J Gly - NH₂ D - Ala - NH₂ .

, F Q Z , Z N -

, H Q Z , F Q Z .

가 :

Ac - Sar - 4 - Cl - D - Phe - D - Nal - Ser - Tyr - D - Pal(Bzl) - Leu - Lys(iPr) - Pro - Ala - NH₂

, 가 :

Ac - D - Nal - 4 - Cl - D - Phe - D - Trp - Ser - Tyr - D - Met(S⁺ Me) - Leu - Arg - Pro - Ala - NH₂

, 가 :

Ac - D - Nal - 4 - Cl - D - Phe - D - Pal - Ser - Tyr - D - Arg - Leu - Met(S⁺ Me) - Pro - Ala - NH₂

LHRH - R

가 :

A - B - C - D - E - F - G - H - I - J

A p - Glu, Ac - D - Nal, Ac - D - Qal, Ac - Sar Ac - D - Pal ,

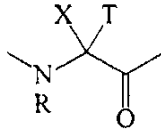
B His 4 - Cl - D - Phe ,

C Trp, D - Pal, D - Nal, L - Nal - D - Pal(N - O) D - Trp ,

D Ser ,

E N - Me - Ala, Tyr, N - Me - Tyr, Ser, Lys(iPr), 4 - Cl - Phe, His, Asn, Met, Ala, Arg Ile ;

F ;



(이때, R 및 X 는 각각 H 또는 알킬이고 ;

T 는 수용체 - 변형 부분을 포함한다.)

G Leu Trp ;

H Lys(iPr), Gln, Met Arg ,

I Pro ;

J Gly - NH₂ D - Ala - NH₂ .

, T , - , ' , ' , ' , ' , T - ' , ' , ' .

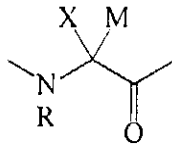
LHRH - R

가 :

A - B - C - D - E - F - G - H - I - J

A pyro - Glu, Ac - D - Nal, Ac - D - Qal, Ac - Sar Ac - D - Pal ,

- B His 4 - Cl - D - Phe ,
 C Trp, D - Pal, D - Nal, L - Nal - D - Pal(N - O) D - Trp ,
 D Ser ,
 E N - Me - Ala, Tyr, N - Me - Tyr, Ser, Lys(iPr), 4 - Cl - Phe, His, Asn, Met, Ala, Arg Ile ;
 F ;



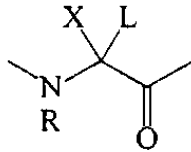
(이때, R 및 X는 각각 H 또는 알킬이고,
 M은 N-아실 친수성 부분을 포함한다.)

- G Leu Trp ;
 H Lys(iPr), Gln, Met Arg ,
 I Pro ;
 J Gly - NH₂ D - Ala - NH₂ .

LHRH - R

가 :
 A - B - C - D - E - F - G - H - I - J

- A pyro - Glu, Ac - D - Nal, Ac - D - Qal, Ac - Sar Ac - D - Pal ,
 B His 4 - Cl - D - Phe ,
 C Trp, D - Pal, D - Nal, L - Nal - D - Pal(N - O) D - Trp ,
 D Ser ,
 E N - Me - Ala, Tyr, N - Me - Tyr, Ser, Lys(iPr), 4 - Cl - Phe, His, Asn, Met, Ala, Arg Ile ;
 F ;



(이때, R 및 X는 각각 H 또는 알킬 이고 ; L은 극성 소부분을 포함한다.)

G Leu Trp ;

H Lys(iPr), Gln, Met Arg ,

I Pro ;

J Gly - NH₂ D - Ala - NH₂ .

, L D - Cit, D - Asn, D - Gln D - Thr .

LHRH (, ED₅₀ 3 µg/Ml, 5 µg/Ml, 10 µg/Ml)
 08/480,494 LHRH PCT WO 96/40757
 - Cl - D - Phe², D - Pal³, N - Me - Tyr⁵, D - Asn⁶, Lys(iPr)⁸, D - Ala¹⁰ - LHRH (PPI - 149 : Ac - D - Nal¹, 4
 WO 96/40757). LHRH - Roeske 4,851,
 385 . LH LHRH , Corbin
 Beattie, Endocrine Res. Commun. 2: 1 (1975)
 LHRH (AOA)
 " " (,)
) Wolfe [Cancer (1976) 37: 2486 - 2492] 가 4 가 . Wolfe
 , N1 ; P1 (subareolar area) (, 1/4)
 1 mm 3 4 mm ; P2 (1/4)
 ; DY 1/2 ,
 P2 DY " " . Wolfe

0 - 2556] Wolfe , Threat [Cancer(1980)45: 255
 , 가 : DY1 : 1/2 ; DY2 :
 1/2 ; DY : 1/2 1/2
 ; QDY : (QDY1) 50 %
 (QDY2), . D
 Y1, DY2, DY QDY2 " " , P2 " "
 , N1, P1 QDY1 " (lucent)"
 가 - [, Boyd,N.F. (1995)J. Natl. Cancer Inst.8
 7: 670 - 675].
 " " (,)
 , " " , , , 가
 (가
),
 " " 가
 (,), , , , , 가
 Jackson,V.P. (1993)Radiology188: 297 - 301 Braeunin
 g,M.P. (1995)Breast Cancer Res. Treat.35: 31 - 38
 " " " "
 LHRH
 , LHRH LHRH (, 가
) LHRH 1 , 1 , 1 - 3
 6 - 24
 LHRH , LHRH
 LHRH LHRH
 1 - 0.01 µg/kg - 10 mg/kg 가 , LHRH
 1 5 - 1000 µg/kg, 10 - 500 µg/kg 10 - 100 µg/kg
 1 30 µg/kg, 50 µg/kg 100 µg/kg

LHRH , LHRH) ,
 (,) ,
 , LHRH
 , PPI - 149
 :
 (PLG). 가
 , Sustained and Controlled Release Drug Delivery Systems, J.R. Robinson, ed., Marcel Dekker, Inc., New York, 1978 (: Lupron^R)
 (4,652,441 4,917,89
 3), 가 (4,849,228), 가
 (4,677,191 4,728,721), (4,675,189).

, LHRH
 . LHRH
 , LHRH
 , 가 (buccal tablets), (troches), , LHRH (wafer
 s) , LHRH

LHRH 가 , LHRH
 가
 (water - in - oil - in - water) CGF [
 Strejan (1984) J. Neuroimmunol. 7: 27]. 가

, 가
 .
 LHRH
 , , , ()
 , 가 , 가

가 (, LHRH)
 ,
 가
 가 가 LHRH
 (PPI - 149/)

가 ,

1 : 1 :

100 µg/kg
iPr⁸,D - Ala¹⁰ - LHRH(PPI - 149)

5 - 1000 µg/kg, 10 -
Ac - D - Nal¹, 4 - Cl - D - Phe², D - Pal³, N - Me - Tyr⁵, D - Asn⁶, Lys(
LHRH

2 : 2 :

LHRH
149 100 Mℓ
CMC , 0.45

USP (100 Mℓ) 0.125 % w/v
[CMC : = 0.2 : 1 (w/w)]

6.25 mg/Mℓ PPI - 149 (CMC)
LHRH PPI - 149

HPLC 가

. 72

95 % PPI - 149

633 mg

57 %

가 가

가

가

(57)

1.

H

LHR

2.

1 , LHRH

1

3.

1 , LHRH

1

4.

1 , LHRH 1 - 3

5.

1 , LHRH 6 - 24

6.

1 , LHRH 1 5 - 1000 µg/kg .

7.

1 , LHRH 1 10 - 500 µg/kg .

8.

1 , LHRH 1 10 - 100 µg/kg .

9.

1 , LHRH 1 .

10.

1 , LHRH .

11.

1 , LHRH .

12.

1 , LHRH 가 : Ac - D - Nal¹, 4 - Cl - D - Phe², D - Pal³, N - Me - Tyr⁵, D - Asn⁶, Lys(iPr)⁸, D - Ala¹⁰ - LHRH.

13.

1 , .

14.

13 , .

15.

13	,	,	,	,	,	,	.
16.							
13	,	LHRH				1	.
17.							
13	,	LHRH				1	.
18.							
13	,	LHRH				1 - 3	.
19.							
13	,	LHRH				6 - 24	.
20.							
13	,	LHRH	1	5 - 1000	$\mu\text{g}/\text{kg}$.
21.							
13	,	LHRH	1	10 - 500	$\mu\text{g}/\text{kg}$.
22.							
13	,	LHRH	1	10 - 100	$\mu\text{g}/\text{kg}$.
23.							
13	,	LHRH	1				.
24.							
13	,	LHRH					.
25.							
13	,	LHRH					.
26.							

13 , LHRH 가 : Ac - D - Nal¹, 4 - Cl - D - Phe², D
 - Pal³, N - Me - Tyr⁵, D - Asn⁶, Lys(iPr)⁸, D - Ala¹⁰ - LHRH.

27.

13 , LHRH 가 : Ac - D - Nal¹, 4 - Cl - D - Phe², D
 - Pal³, Tyr⁵, D - Asn⁶, Lys(iPr)⁸, D - Ala¹⁰ - LHRH.

28.

:

LHRH

LHRH

29.

28 , LHRH

30.

28 , LHRH

31.

28 , LHRH

32.

28 , LHRH 가 : Ac - D - Nal¹, 4 - Cl - D
 - Phe², D - Pal³, N - Me - Tyr⁵, D - Asn⁶, Lys(iPr)⁸, D - Ala¹⁰ - LHRH.

33.

28 , LHRH 가 : Ac - D - Nal¹, 4 - Cl - D
 - Phe², D - Pal³, Tyr⁵, D - Asn⁶, Lys(iPr)⁸, D - Ala¹⁰ - LHRH.