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(12)

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A61K 31/41

A61K 31/4184

A61K 31/435

A61K 31/44

(11)

(43)

10-2005-0000546

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(87)

WO 2003/097045

(86) 2003 05 16

(87)

2003 11 27

(30)	60/381,547	2002 05 17	(US)
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(71)

- 4056

35

(72)

07931

12

08822

17

(74)

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(54)

[illegible]

가

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(*Campo C,*

Segura J, Ruilope LM, J Clin Hypertens (Greenwich) 2002 Jan, 4(1):35-40).

(Collins R, Peto R, MacMahon S, Hebert P, Fiebach NH, Eberlein KA, Godwin J, Qizilbash N, Taylor JO, Hennekens CH, Lancet 1990, 335(8693):827-38).

가 (Waeber B, Brunner HR, Am J, Hypertens 1997, 10(7 Pt 2):131S-137S).

가 (MacGregor GA, Markandu ND, Banks RA, Bayliss J, Roulston JE, Jones JC, Br Med J (Clin Res Ed), 284 (6317): 693-6).

(i) E-4177, SC-52458 ZD8731, (1, AT₁) (ARB);
(ii) (CCB);
(iii)

가 (i) (ARB), (ii) (CCB), (iii)

(i) E-4177, SC-52458 ZD8731 ARB,
; (ii) (DHP),
-DHP CCB CCB, (iii)
()
(), (-),
(Raynaud's disease), (),

가 (i) E-4177, SC-52458 ZD8731 ARB,
; (ii) (DHP),
-DHP CCB CCB, (iii)
()
(-), ()
(),

2 3 ,

ARB , CCB

CCB ARB

(, ,

) , ,

((i) (iii)

2 3 , ()

CE (i), CCB (ii) ARB (i) (iii)가 - (, Co-DIOVAN) , A

(, Norvasc)

%, 1% , 80% , 0.1% 90

가 ,

가 ,

가 ,

()

ARB + CCB + 1 20 mg 900 mg 75 kg ,

CCB ARB ,

(HCTZ) . 가

(i) ARB, (ii) CCB (iii) HCTZ , , 가 HCTZ

(baseline) (mmHg) (AUC) (,)

: (trough:peak) (first-dose)

1 .

(distensibility) , (compliance)

가 ,

HCTZ

HCTZ , H

CTZ , HCTZ

HCTZ (responder)

HCTZ

(, , - , , , ,)

(,)

[illegible]

(Plexiglas home cage)

:

DOCA

7-10

(M.K. Bazil, C. Krulan and R.L. Webb., Telemetric monitoring cardiovascular parameters in conscious spontaneously hypertensive rats, J. Cardiovasc. Pharmacol. 22: 897-905, 1993)

24

3

9

(1-3 mg/kg),

2

8

1 100 mg/kg/
75 mg/kg/

1 75 mg/kg/ , HCTZ 1

가 , SHR
(background) RAAS

HCTZ

SHR
RAAS

가

(Taconic Farms, Germantown, New York)

(SHR)(Tac:N(SHR)fBR)
, Minnesota) 14 16

(Data Sciences International, Inc., St. Paul
SHR

2

(receiver)

(, SHR)

SHR

10

10

24

144-10

3

24

가

, 12

(gavage)

1

5

HCTZ

3

4

1

75 mg/kg/

, HCTZ

1

1 100 mg/kg/
75 mg/kg/

1

100 mg/kg/

1

30 mg/kg/

HCTZ 50

mg/kg/

CTZ

가

75 mg/kg/

1

50 mg/kg/

H

, SHR DOCA-
(atrial appendages)

+ ()

가

가

SHR (Intengan HD, Thibau

It G, Li JS, Schiffrin EL, Circulation 1999, 100 (22): 2267-2275)

OCA-

가

(Intengan HD, Park JB, Schiffrin EL, Hypertension, 1999,

34 (4 Part 2): 907-913)

가 (Ceiler

DL, Nelissen-Vrancken HJ, De Mey JG, Smits JF, J Cardiovasc Pharmacol 1998, 31(4):630-7)
 (Nagura J, Yamamoto M, Hui C, Yasuda S, Hachisu M, Konno F, Clin Exp Pharmacol Physiol 1996, 23(3):229-35)
 가
 (Nabata H, Aono J, Ishizuka N, Sakai K, Arch Int Pharmacodyn Ther 1985, 277(1):104-18)
 SHR 가
 acolley P, Poitevin P, Koen R, Levy BI, J Hypertens 1998, 16(3):349-55) 가

20 320 mg, 640 mg
 40 mg 1 1 80 mg 1 160 mg 320 mg 640 mg
 가 3 80 mg 160 mg
 q.d. b.i.d.

mg, 2.5 20 mg, 2.5 10 mg 1 mg 60

HCTZ
 00 mg, 50 mg 150 mg, 25 mg 100 mg, 5 mg 2
 5 mg 25 mg

60 100 mg, 80 mg , 2 12 mg, 2.5 5 mg
 8 16 mg, 12.5 mg HCTZ

5 10 mg 140 180 mg, 160 mg , 2 12 mg, 2.5
 8 16 mg, 12.5 mg HCTZ

10 mg 140 180 mg, 160 mg , 4 12 mg, 5 mg
 20 30 mg, 25 mg HCTZ

(i) ARB, (ii) CCB (iii)

가
 , 1 1 , 1 2 3 가 가
 가

(i) (iii) 가 ,

(, Diovan) HCTZ
 (, Co-DIOVAN) (, Norvasc)

1 :

(, Diovan)

	(mg)				¹ (kg)			
	40 mg	80 mg	160 mg	320 mg	40 mg	80 mg	160 mg	320 mg
	40.000	80.000	160.000	320.000	144.000	144.000	144.000	144.000

(NF, Ph.Eur.) PH102	27.000	54.000	108.000	216.000	97.200	97.200	97.200	97.200
(NF, Ph.Eur.)	7.500	15.000	30.000	60.000	27.000	27.000	27.000	27.000
(Ph.Eur.)/ (F)/ 200	(N) 0.750	1.500	3.000	6.000	2.700	2.700	2.700	2.700
(NF, Ph.Eur.)	1.500	3.000	6.000	12.000	5.400	5.400	5.400	5.400
(NF, Ph.Eur.)	0.750	1.500	3.000	6.000	2.700	2.700	2.700	2.700
(DIOLACK Gelb) F32892	2.800				11.090 ²			
(DIOLACK Blassrot) F34899		6.000				12.420 ³		
(DIOLACK H ellbraun) F33172			9.000				9.720 ⁴	
(DIOLACK Bra un) F16711				16.000				8.640 ⁴
					62.843	70.380	55.080	48.960
/	80.300	161.000	319.000	636.000	289.080	289.800	287.100	286.200
1.	2							
2.		10%			.			
3.		15%			.			
4.		20%			.			

(Diolack)

	HPMC USP/Ph. Eur.(60 3)	PEG 80 00 USP/P h. Eur.	() USP/Ph. Eur.	() Ph.Fr./NF/E172/CFR /CI 77491	() Ph.Fr./NF/E172/CFR /CI 77492	()	() E172/CFR/ CI 77499
(Gelb) F32892	80.00%	4.00%	13.48%	0.01%	2.50%	-	0.01%
(Blassrot) F34899	80.00%	4.00%	15.50%	0.40%	0.10%	-	-
(Hellbrau n) F33172	80.00%	4.00%	9.34%	0.25%	6.40%	-	0.01%

(Br aun) F167 11	80.00%	4.00%	14.00%	0.50%	0.50%	0.50 %	0.50%
------------------------	--------	-------	--------	-------	-------	-----------	-------

erosile) 200 , , , / / (A
(screening mill)
(roller compactor)
/ 200 가 , (blend)

2 :

- (, Co-DIOVAN)

	(mg)	(mg)	(mg)
	80.000	160.000	160.000
(Esidrex) ()	12.500	12.500	25.00
(NF, Ph.Eur.)/ PH102	31.500	75.500	63.00
(NF, Ph.Eur.)	20.000	40.000	40.00
(Ph.Eur.)/ (NF)/ 200	1.500	3.00	3.00
(NF, Ph.Eur.)	3.000	6.000	6.00
(NF, Ph.Eur.)	1.500	3.000	3.00
(Opadry Black) OOF17713	-	-	0.096
(Opadry Red) OOF15613	-	-	0.762
(Opadry Yellow) OOF12951	-	-	3.808
(Opadry White) OOF18296	-	-	5.334
	2.76	5.510	-
	0.025	-	-
	0.025	0.750	-
8000	0.50	1.000	-
	2.000	3.990	-
	0.70	0.750	-
/	156.00	312.000	310.000

(Opadry)

	HPMC USP/Ph.	PEG 4000 USP/Ph.	USP/	()	()	()
--	-----------------	---------------------	------	-----	-----	-----

		Eur. (603)	Eur.	Ph.Eur.	() USP/Ph. Eur.()	Ph.Fr./NF/ E172/CFR/ CI 77491	Ph.Fr./NF/ E172/CFR/ CI 77492	E172/CFR/ CI 77499
96 *	OOF182	71.4%	7.15%	7.15%	14.3%	-	-	-
3 *	OOF1561	71.4%	7.15%	7.15%	-	14.3%	-	-
3 *	OOF1561	71.4%	7.15%	7.15%	-	-	14.3%	-
3 *	OOF1771	71.4%	7.15%	7.15%	-	-	-	14.3%

(Aerosile) 200 (Esidrex) (), , , 가

3 :

	(mg)	(%)
	80.00	43.02
	6.94	3.73
102 (I)	54.00	29.04
102 (II)	20.00	10.76
(I)	15.00	8.07
(II)	4.0	2.15
- - (Cab-O-Sil)	1.50	0.81
(I)	3.00	1.61
(II)	1.50	0.81
	185.94	100.00

(57)

1.

(i) (ARB) _____,

(ii) (CCB) ,

(iii)

2.

1. (i) (ARB)가 E-4177, SC-52458 ZD8731
; (ii) (CCB)가
; (iii) 가

3.

2. (i) (ARB)가 ; (ii) (CCB)가 ; (iii) 가 .

4.

3, 20, 640 mg, 1 mg, 60 mg
5 mg, 200 mg.

5.

4, 40, 320 mg, 2.5 mg, 10 mg, 5 mg, 25 mg.

6.

(i) (ARB) ,

(ii) (CCB) ,

(iii)

(i)	(iii)	2	3
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7.

6 (i) (ARB)가 E-4177, SC-52458 ZD8731
; (ii) (CCB)가
; (iii) 가

8.

7. (i) (ARB)가 ; (ii) (CCB)가 ; (iii) 가 .

9.

8, 20, 640 mg, 1 mg, 60 mg, 5 mg, 200 mg.

10.

9, 40, 320 mg, 2.5 mg, 10 mg, 5 mg, 25 mg.

11.

(i) , , , , , , ,

, E - 4177, SC - 52458 ZD8731

ARB

•
;

(ii) 

(iii)

가

()

() , (-) ,

aynaud's disease), () , (R

12.

[illegible]

13.

12 (i) (ARB)가 ; (ii) (CCB)가
; (iii) 가 .

14.

13 (ARB)(i) (iii)가 - (, Co-DIOVAN)
(ARB)(i), CCB (ii) (iii)가 - (, Co-DIOVAN)
(, Norvasc) .

15.

101

1

2

3

4

5

6

7

8

9

10

16.

, () ,
 , (), (-), , , ,
 , , , , , , , , ,
 , (5), , 6 10
 1 5 .