



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/EP99/08972 (22) International Filing Date: 20 November 1999 (20.11.99) (30) Priority Data: 98122489.2 27 November 1998 (27.11.98) EP (71) Applicant: F. HOFFMANN-LA ROCHE AG [CH/CH]; 124, Grenzacherstrasse, CH-4070 Basle (CH). (72) Inventor: HELLER, Rudolf; Lindenberg 7, A-2123 Traunfeld (AT). (74) Agent: WITTE, Hubert; 124, Grenzacherstrasse, CH-4070 Basle (CH).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> (88) Date of publication of the international search report: 16 November 2000 (16.11.00)
(54) Title: PHARMACEUTICAL COMBINATION PREPARATIONS OF CARVEDILOL AND HYDROCHLOROTHIAZIDE (57) Abstract The present invention is concerned with a pharmaceutical combination preparation for the treatment of cardiac and cardiovascular disorders such as hypertension, angina pectoris, cardiac insufficiency and illnesses associated therewith, containing the active substances carvedilol or a pharmaceutically acceptable salt thereof and hydrochlorothiazide or a pharmaceutically acceptable salt thereof as well as pharmaceutically usual additives.		

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INTERNATIONAL SEARCH REPORT

Inter: nal Application No
PCT/EP 99/08972

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61K31/54 A61K31/403 A61K9/28 //(A61K31/54,31:40)				
According to International Patent Classification (IPC) or to both national classification and IPC				
B. FIELDS SEARCHED				
Minimum documentation searched (classification system followed by classification symbols) IPC 7 A61K				
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched				
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EMBASE, MEDLINE, EPO-Internal, BIOSIS, CHEM ABS Data, CANCERLIT, PAJ, WPI Data				
C. DOCUMENTS CONSIDERED TO BE RELEVANT				
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.		
X	BISTON P. ET AL: "Carvedilol in the treatment of mild to moderate hypertension: Experience with ambulatory blood pressure monitoring." ACTA CARDIOLOGICA, (1994) 49/2 (145-155)., XP000904756 page 146, paragraph 5 page 154, paragraph 3 ---	1-4,7,8		
X	RUDORF J.E. ET AL: "Pharmacokinetic and pharmacodynamic interactions of combined acute administration of carvedilol and hydrochlorothiazide in hypertensive volunteers." DRUGS, (1988) 36/SUPPL. 6 (113-117)., XP000904788 page 117, column 1, paragraph 2 -column 2, paragraph 1 --- -/---	1-4,7,8		
<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none;"> <input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. </td> <td style="width: 50%; border: none;"> <input checked="" type="checkbox"/> Patent family members are listed in annex. </td> </tr> </table>			<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.	<input checked="" type="checkbox"/> Patent family members are listed in annex.
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<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none;"> "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed </td> <td style="width: 50%; border: none;"> "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family </td> </tr> </table>			"A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family
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Date of the actual completion of the international search <h2 style="text-align: center;">22 August 2000</h2>		Date of mailing of the international search report <h2 style="text-align: center;">05. 09. 2000</h2>		
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer <h2 style="text-align: center;">Marttin, E</h2>		

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/08972

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DUPONT A G ET AL: "The safety of adding carvedilol to hypertensive patients inadequately treated with diuretics." EUROPEAN JOURNAL OF CLINICAL PHARMACOLOGY, (1990) 38 SUPPL 2 S153-7., XP000904769 page 157, column 1, paragraph 2 ---	1-4,7,8
X	WIDMANN L ET AL: "Safety and antihypertensive efficacy of carvedilol and atenolol alone and in combination with hydrochlorothiazide." EUROPEAN JOURNAL OF CLINICAL PHARMACOLOGY, (1990) 38 SUPPL 2 S143-6., XP000904786 figure 1 page 145, column 2, paragraph 6 -page 146, column 2, paragraph 1 ---	1-4,7,8
X	WO 96 24348 A (BOEHRINGER MANNHEIM PHARM CORP ;LUKAS LASKEY MARY ANN (US); RUFFOL) 15 August 1996 (1996-08-15) page 9, line 9 - line 26 ---	1-4,7,8
X	DE 196 37 082 A (BOEHRINGER MANNHEIM GMBH) 19 March 1998 (1998-03-19) page 2, line 65 - last line page 3, line 7 - line 9 page 3, line 24 - line 32 page 3, line 46 - line 55; claims 1-3,5,7,10; examples 1-19,21-25 ---	18,19,22
X	WO 98 05320 A (BENKERROUR LOUTFY ;JOUVEINAL LAB (FR); DOAT BERNARD (FR)) 12 February 1998 (1998-02-12) page 8, line 10 - line 25; claims 1-6; example 1 ---	18,22
A		19
X	US 5 425 950 A (DANDIKER YOGENDRA ET AL) 20 June 1995 (1995-06-20) column 3, line 17 - line 33 column 6, line 5 - line 32; claims 1,2,8,9; examples 1,2,4,9 ---	18,22
A		19
A	THOENNES C J ET AL: "EVALUATION OF A RAPIDLY DISINTEGRATING MOISTURE RESISTANT LACQUER FILM COATING" DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, vol. 15, no. 2, 1989, pages 165-186, XP000938464 ISSN: 0363-9045 abstract page 166, paragraph 2; table 3 ---	20-22
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International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>"Eudragit E30D Anwendung in der Arzneimittelherstellung" May 1981 (1981-05), RÖHM PHARMA , WEITERSTAT XP002145397 page 4, column 2, line 1 -page 5, column 2, last line</p> <p style="text-align: center;">---</p>	20-22
A	<p>US 5 019 398 A (DASTE GEORGES) 28 May 1991 (1991-05-28) column 2, line 47 - line 63; claims; examples</p> <p style="text-align: center;">-----</p>	20-22

INTERNATIONAL SEARCH REPORT

International application No.
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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 8 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: -
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claim 22 does not meet the requirements of Article 6 PCT in that the subject-matter for which protection is sought is not clearly defined. A lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear (and/or concise), namely claim 22 insofar as a composition according to claims 1-21 was concerned.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-17, 22 (partially)

The problem to be solved by the present application is to provide a pharmaceutical combination for the treatment of cardiac or cardiovascular disorders.

The solution to this problem proposed in the present application is to use a combination containing the active substances carvediol or a pharmaceutically acceptable salt thereof and hydrochlorothiazide or a pharmaceutically acceptable salt thereof.

The subject matters of claim 18-19 or 20-21 are no solutions to the mentioned problem: These claims are concerned with a pharmaceutically acceptable solid dosage form having a disintegrant content of at least 5 weight% or with a light-protecting film suspension.

The idea to use a combination of carvediol and hydrochlorothiazide is known in the state of the art (see the documents cited in the search report), and cannot serve as a single inventive concept, linking the different inventions.

In the present application no further technical features can be distinguished that can be regarded as a "special technical feature" involved in the technical relationship among the different inventions. Consequently, the present application lacks unity of invention, and the different solutions not belonging to a common inventive concept are identified as the different subjects listed above.

Searching these different subjects would have caused a major additional searching effort. Only the first subject was searched.

2. Claim : 18 19 22 (partially)

A pharmaceutically acceptable solid dosage form having a disintegrant content of at least 5 weight%

3. Claim : 20 21 22 (partially)

A light-protecting film suspension.

INTERNATIONAL SEARCH REPORT

 International Application No
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date		
WO 9624348 A	15-08-1996	DE 19503995 A	22-08-1996		
		US 5760069 A	02-06-1998		
		AT 179891 T	15-05-1999		
		AU 702106 B	11-02-1999		
		AU 4718196 A	27-08-1996		
		BR 9607111 A	04-11-1997		
		CA 2212548 A	15-08-1996		
		CN 1185106 A	17-06-1998		
		CZ 9702463 A	11-11-1998		
		DE 69602424 D	17-06-1999		
		DE 69602424 T	07-10-1999		
		EP 0808162 A	26-11-1997		
		ES 2134588 T	01-10-1999		
		FI 973255 A	07-08-1997		
		GR 3030966 T	30-11-1999		
		HU 9900773 A	28-07-1999		
		JP 10513463 T	22-12-1998		
		NO 973667 A	08-08-1997		
		PL 321737 A	22-12-1997		
		SI 808162 T	31-10-1999		
		SK 106897 A	10-03-1999		
US 5902821 A	11-05-1999				
DE 19637082 A	19-03-1998	AU 4553997 A	02-04-1998		
		CN 1237104 A	01-12-1999		
		WO 9810754 A	19-03-1998		
		EP 0925060 A	30-06-1999		
		ZA 9708171 A	11-03-1999		
WO 9805320 A	12-02-1998	FR 2752162 A	13-02-1998		
		AU 3697097 A	25-02-1998		
		BR 9711032 A	17-08-1999		
		CA 2256751 A	12-02-1998		
		CN 1226162 A	18-08-1999		
		CZ 9900376 A	12-05-1999		
		EP 0942718 A	22-09-1999		
		ES 2130081 A	16-06-1999		
		GR 1002907 B	13-05-1998		
		HU 9902878 A	28-04-2000		
		IT GE970067 A	08-02-1999		
		PL 331517 A	19-07-1999		
		PT 102031 A	27-02-1998		
		US 5425950 A	20-06-1995	AU 666880 B	29-02-1996
				AU 2746992 A	06-05-1993
BE 1005490 A	10-08-1993				
CA 2081709 A	01-05-1993				
CH 685536 A	15-08-1995				
CZ 9203257 A	13-10-1993				
DE 69222006 D	09-10-1997				
DE 69222006 T	22-01-1998				
EP 0546593 A	16-06-1993				
ES 2106818 T	16-11-1997				
FR 2683146 A	07-05-1993				
GB 2262445 A,B	23-06-1993				
IT 1263253 B	05-08-1996				
JP 5194188 A	03-08-1993				
LU 88186 A	17-05-1993				

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/08972

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5425950 A		MX 9206236 A	01-04-1993
		NO 924183 A	03-05-1993
		NZ 244921 A	27-04-1995
		ZA 9208359 A	13-08-1993

US 5019398 A	28-05-1991	FR 2643556 A	31-08-1990
		AU 623225 B	07-05-1992
		AU 4999890 A	30-08-1990
		CA 2010427 A	27-08-1990
		DE 69000881 D	25-03-1993
		DE 69000881 T	12-08-1993
		EP 0385846 A	05-09-1990
		NZ 232649 A	29-01-1991
