PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 31/40, 47/00	A1	(11) International Publication Number: **WO 00/04902**
		(43) International Publication Date: 3 February 2000 (03.02.00)

(21) International Application Number: PCT/EP99/04974

(22) International Filing Date: 14 July 1999 (14.07.99)

(30) Priority Data:
198 33 119.3 23 July 1998 (23.07.98) DE

(71) Applicant *(for all designated States except US)*: ROCHE DIAGNOSTICS GMBH [DE/DE]; Sandhofer Strasse 116, D–68305 Mannheim (DE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: GRUBER, Werner [DE/DE]; Riedackerweg 2, D–69488 Birkenau (DE). WOOG, Heinrich [DE/DE]; Lindenstrasse 6, D–69514 Laudenbach (DE).

(74) Agent: WITTE, Hubert; Grenzacherstrasse 124, 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, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, 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
With international search report.

(54) Title: STABILIZED CARVEDILOL INJECTION SOLUTION

(57) Abstract

The object of the invention are ready–to–inject, aqueous injection solutions containing carvedilol (1–(9H–carbazolyl–4–yloxy)–3–[[2–(2–methoxyphenoxy)ethyl]–amino]–2–propanol) or its pharmacologically harmless salts as well as a process for their production. The injection solutions are stable on storage and are well tolerated by veins.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

STABILIZED CARVEDILOL INJECTION SOLUTION

The object of the invention are ready-to-inject, aqueous injection solutions containing carvedilol (1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-2-propanol) or its pharmacologically harmless salts as well as a process for their production. The injection solutions are stable on storage and are tolerated well by veins.

Carbazol-4-yloxy-propanolamine derivatives as well as their pharmacologically harmless salts, which exhibit vasodilating and β-receptor blocking activities in pharmacological tests and which are suitable for the treatment and prophylaxis of circulatory and cardiac disorders such as hypertension and angina pectoris, are known from EP 0 004 920.

Carvedilol and carvedilol derivatives are also described by Yue et al. in "The Journal of Pharmacology and Experimental Therapeutics" 236 (1), pages 92-98 (1992). The authors report that carvedilol and especially carvedilol derivatives which are hydroxylated in the carbazole structure or in the phenoxy ring exhibit an antioxidative activity and inhibit lipid peroxidation.

Although enteral, parenteral and oral dosage forms are proposed in EP 0 004 920, only oral dosage forms have hitherto been developed successfully. There has, indeed, been a series of experiments to incorporate carvedilol into conventional injectable preparations. However, these have hitherto surprisingly come to nothing. It has been found that such preparations are either not tolerated by veins or are not sufficiently stable, so that in the case of lengthy storage the solutions recrystallize or decomposition products are formed. These negative phenomena thus exclude use for injection purposes.

The solubility of carvedilol in water is about 0.2 mg/100 ml, i.e. 0.002 mg/ml, with a pH value of 6.1 resulting. This solubility is, of course, not sufficient to achieve the therapeutically required dosage of an injection solution in the order of several mg/ml. Upon standing, supersaturated solutions precipitate carvedilol crystals after a short period, so that they are unsuitable as ready-to-inject injection solutions. An increase in the acidity to pH values of 1 to 3 indeed prevents the crystallization of the carvedilol and increases the

dissolved amount of the active substance, but leads to an intolerance of the solutions by veins. Moreover, decomposition products form therefrom after a short period. These decomposition products also mean that such a solution can not be used for injection purposes.

Long-term medication with carvedilol has accordingly hitherto been carried out predominantly in the form of solid dosage forms such as tablets and capsules. It would, however, also be desirable, especially for clinical uses, to provide readily injectable dosage forms. In order, in use, not to have to rely on the necessity of firstly mixing the components with one another, e.g. in the case of a lyophilizate, such an injection solution should be as "ready-to-inject" as possible. In other words, all required components should already be present in the correct ratios in the ampoule solution.

The object of the invention was to find a formulation in order to provide carvedilol or its pharmacologically harmless salts as injection solutions having therapeutically relevant concentrations, with the injection solutions being stable on storage and being tolerated well by veins.

Surprisingly, stable, vein-tolerable and high dosage injection solutions containing carvedilol or its pharmacologically harmless salts are obtained when on the one hand a physiologically compatible acidic buffer having a pH value between 7.2 and 4.0 and on the other hand an organic solvent, such as, for example, polyethylene glycol, is added to the solution. It is also necessary to add an antioxidant and an agent which binds metal ions.

The ready-to-inject injection solutions containing carvedilol or its pharmacologically harmless salts in accordance with the invention contain a physiologically compatible buffer having a pH value of 7.2 to 4.0, a water-soluble organic solvent, an antioxidant as well as an agent which binds heavy metals.

The carvedilol concentration in the ready-to-inject injection solutions is preferably 1 to 5 mg/ml.

Examples of pharmacologically harmless salts are salts of carvedilol with inorganic or organic acids, such as e.g. hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, acetic acid, citric acid, maleic acid or benzoic acid.

The injection solutions in accordance with the invention have a pH value of 4.0 to 7.4, preferably from 4.4 to 7.0.

Amounts of active substance and adjuvants are chosen such that isotonic injection solutions are obtained as far as possible. In the event that this is not already guaranteed by the available components, other adjuvants which are customary for this purpose, such as e.g. sodium chloride, fructose, glucose etc., can also be added to adjust the isotonicity.

Organic solvents which are preferably used are ethanol and solvents which have a degree of polymerization. Solvents which have a degree of polymerizaton in accordance with the invention are preferably trimethylene glycol and polyethylene glycol. Polyethylene glycol with a molecular weight between 100 and 1,500, particularly 200 to 600, has been found to be especially preferred. The organic solvent is usually added in an amount of 5 to 25 wt.%, with an addition of about 10 wt.% being preferred.

Physiologically compatible buffer substances in accordance with the invention are, for example, weak acids, such as acetic acid, malic acid, carbonic acid, phosphoric acid or amino acids. In particular, the sodium, potassium or ammonium salts of the acids such as the acetate, malate, carbonate, phosphate, glycinate, arginate or other amino acid salts come into consideration.

A special case of buffering comprises adding a further active substance which acts as a buffer to the aforementioned buffers. As the carvedilol injection solutions in accordance with the invention are stable in the acidic to neutral range, there exists the possibility of incorporating a loop diuretic in the formulations in addition to the β-blocker carvedilol. Torasemide, azosemide and furosemide are preferably used as loop diuretics, and in these aqueous injection solutions the organic solvents such as polyethylene glycol, trimethylene glycol or ethanol can be present in a maximum amount of 25%. The solubility of the loop diuretics in these acidic to maximum neutral formulations is as follows:

Torasemide from 1 mg/ml to 2 mg/ml
azosemide from 1 mg/ml to 3 mg/ml
furosemide from 1 mg/ml to 5 mg/ml

The furosemide, torasemide or azosemide is preferably added in the form of the sodium or potassium salt.

Preferred buffer substances present in the ready-to-inject injection solutions are sodium, potassium or ammonium salts of weak acids and/or loop diuretics or their sodiu or potassium salts, with torasemide, azosemide or furosemide being especially preferred as the loop diuretic.

As the antioxidant there can be used any additive which is effective in an acidic medium and which is suitable for injection solutions, e.g. inorganic or organic sulphur compounds, such as e.g. methionine or sodium disulphide, or ascorbic acid in the form of sodium ascorbate. Methionine is preferably used in accordance with the invention, especially in a concentration of 1 to 10 mg/ml, preferably of 2 to 5 mg/ml.

The optimal stabilization of the formulation is guaranteed surprisingly by an agent which binds heavy metal ions, such as e.g. a complex former which inactivates heavy metal ions, preferably EDTA (ethylenediaminetetraacetic acid, edetic acid) or its disodium salt (Titriplex III). It has surprisingly been found that the solvent-containing carvedilol solutions are only sufficiently stable and endure a sterilization for 20 minutes in the final container at 121°C without decomposition when the combination of antioxidant and heavy metal ion binder is guaranteed. The concentration of the complex former is 0.1 to 10 mg/l, preferably 0.1 to 0.3 mg/ml.

In a preferred embodiment of the invention injection solutions, which are used for intravenous administrations, have a buffer capacity of up to 5 mVal/l, preferably up to 1 mVal/l, particularly from 0.3 mVal/l up to 0.1 mVal/l, especially up to 0.05 mVal/l.

Furthermore, the ready-to-inject vein-compatible injection solution advantageously has a titration basicity which is as low as possible, namely from 10 to 0.05 mmol/l, especially from 1.0 to 0.05 mmol/l.

Preferred limits for the titration basicity of the injection solutions for successful intravenous administration are up to 10 ml, preferably up to 5 ml, especially up to 3 ml and particularly up to 1 ml, of a 0.1N NaOH solution. This corresponds to a titration basicity up to 1 mmol/l, especially up to 0.3 mmol/l, particularly up to 0.1 mmol/l.

The titration acidity or basicity is generally defined as that amount of acid or alkali which is required to adjust the pH value in a solution having a volume of 1 l to the pH value of blood (about 7.0 to 7.4).

The method for the determination of the titration basicity is carried out in an analogous manner to the determination of the buffer capacity by starting from the finished administerable injection solution or infusion solution and determining that amount of base which is required to adjust the pH value of the solution to about 7.0 to 7.4.

The production of the injection solution in accordance with the invention is preferably effected by suspending the active substance in the organic solvent with part of the required water and dissolving the active substance by the addition of the appropriate amount of buffer substance. Thereafter, the solution is, if necessary, adjusted to the desired pH value of 4.0 to 7.4 by the addition of small amounts of alkali. The antioxidant and the agent which binds heavy metal ions are added in dissolved form, the injection solution is optionally provided with additional additives to adjust the isotonicity and made up to the final volume with water.

In order to achieve a reduction in the oxygen content of the injection solution in accordance with the invention, continuous gasification with nitrogen is preferably carried out during the production of the injection solution batch. The nitrogen gasification is continued not only during the sterile filtration, but also when the injection solution is drawn from the ampoule.

Of course, as an alternative the isolated carvedilol salt can also be used directly. The thus-obtained solution is filtered over a sterile filter having a pore diameter of 0.2 µm and thereafter filled into ampoules on an automatic ampoule filling machine while gassing with nitrogen and sterilized in an autoclave at 121°C for 20 minutes. The ampoules are usually filled under nitrogen and can be stored at room temperature for at least 3 years without the occurrence of turbidity and without the active substance being chemically changed to a significant extent.

Having regard to the low buffer capacity and low titration basicity, the injection solutions in accordance with the invention have a very good vein tolerance and do not lead to significant pH changes at the injection site, so that an undiluted administration is possible, whereby the buffer capacity of the solutions should be lower than 5 mVal/ml solution, i.e. the pH value is brought to a pH value of 7 to 7.5 by the addition of a corresponding amount of 0.1N sodium hydroxide solution.

The solutions in accordance with the invention are ready-to-inject and can be injected directly. It is, however, likewise possible to admix them with an isotonic glucose or saline solution and to infuse.

The invention is illustrated in more detail in the following Examples.

Examples of carvedilol injection solutions (in each case for 1000 ampoules)

Example 1

Carvedilol	5.00 g
Acetic acid 100 %	2.00 g
Polyethylene glycol (macrogol 400)	500.00 g
Methionine	10.00 g
Titriplex III	0.50 g
Water for injection ad	5.00 l

2.5 l of water for injection are placed in a vessel of sufficient size which is provided with a stirrer and macrogol is dissolved therein while stirring and under N_2 gasification. The carvedilol is suspended in the mixture while stirring vigorously and dissolved by the addition of acetic acid. The pH value is adjusted to 4.4 to 4.8 with 1N NaOH, methionine and Titriplex III are dissolved and the mixture is made up with water for injection to the final volume.

The solution is filtered over a 0.2 µm membrane filter or filter candle, filled into ampoules on a suitable filling machine under N_2 gasification and sterilized for 20 minutes at 121°C in a steam sterilizer.

Example 2

Carvedilol	5.00 g
Acetic acid	2.00 g
Propylene glycol	600.00 g
Methionine	10.00 g
Titriplex III	0.50 g
Water for injection ad	5.00 l

2.5 l of water for injection are placed in a vessel of sufficient size which is provided with a stirrer and propylene glycol is dissolved therein while stirring and under N_2 gasification. The carvedilol is suspended in the mixture while stirring vigorously and dissolved by the addition of acetic acid. The pH value is adjusted to 4.4 to 4.8 with 1N NaOH, methionine and Titriplex III are dissolved and the mixture is made up with water for injection to the final volume.

The solution is filtered over a 0.2 µm membrane filter or filter candle, filled into ampoules on a suitable filling machine under N_2 gasification and sterilized for 20 minutes at 121°C in a steam sterilizer.

Example 3:

Carvedilol	5.00 g
Malic acid	2.00 g
Polyethylene glycol (macrogol 400)	500.00 g
Methionine	10.00 g
Titriplex III	0.50 g
Water for injection ad	5.00 l

2.5 l of water for injection are placed in a vessel of sufficient size which is provided with a stirrer and macrogol is dissolved therein while stirring and under N_2 gasification. The carvedilol is suspended in the mixture while stirring vigorously and dissolved by the addition of malic acid. The pH value is adjusted to 4.4 to 4.8 with 1N NaOH, methionine and Titriplex III are dissolved and the mixture is made up with water for injection to the final volume.

The solution is filtered over a 0.2 µm membrane filter or filter candle, filled into ampoules on a suitable filling machine under N_2 gasification and sterilized for 20 minutes at 121°C in a steam sterilizer.

Example 4:

Carvedilol	5.00 g
Citric acid H_2O	2.00 g
Polyethylene glycol (macrogol 400)	500.00 g
Methionine	10.00 g
Titriplex III	0.50 g
Water for injection ad	5.00 l

2.5 l of water for injection are placed in a vessel of sufficient size which is provided with a stirrer and macrogol is dissolved therein while stirring and under N_2 gasification. The carvedilol is suspended in the mixture while stirring vigorously and dissolved by the addition of citric acid. The pH value is adjusted to 4.4 to 4.8 with 1N NaOH, methionine and Titriplex III are dissolved and the mixture is made up with water for injection to the final volume.

The solution is filtered over a 0.2 µm membrane filter or filter candle, filled into ampoules on a suitable filling machine under N_2 gasification and sterilized for 20 minutes at 121°C in a steam sterilizer.

Example 5:

Carvedilol	5.00 g
Malic acid	2.00 g
Propylene glycol	600.00 g
Methionine	10.00 g
Titriplex III	0.50 g
Water for injection ad	5.00 l

2.5 l of water for injection are placed in a vessel of sufficient size which is provided with a stirrer and propylene glycol is dissolved therein while stirring and under N_2 gasification. The carvedilol is suspended in the mixture while stirring vigorously and dissolved by the addition of malic acid. The pH value is adjusted to 4.4 to 4.8 with 1N NaOH, methionine and Titriplex III are dissolved and the mixture is made up with water for injection to the final volume.

The solution is filtered over a 0.2 µm membrane filter or filter candle, filled into ampoules on a suitable filling machine under N_2 gasification and sterilized for 20 minutes at 121°C in a steam sterilizer.

Example 6:

Carvedilol	5.00 g
Malic acid	2.00 g

Torasemide	10.00 g
Poylethylene glycol (macrogol 400)	500.00 g
Methionine	10.00 g
Titriplex III	0.50 g
Water for injection ad	5.00 l

2.5 l of water for injection are placed in a vessel of sufficient size which is provided with a stirrer and macrogol is dissolved therein while stirring and under N_2 gasification. The carvedilol is suspended in the mixture while stirring vigorously and dissolved by the addition of malic acid and the toresamide. The pH value is adjusted to 4.4 to 4.8 with 1N NaOH, methionine and Titriplex III are dissolved and the mixture is made up with water for injection to the final volume.

The solution is filtered over a 0.2 µm membrane filter or filter candle, filled into ampoules on a suitable filling machine under N_2 gasification and sterilized for 20 minutes at 121°C in a steam sterilizer.

Example 7:

Carvedilol	5.00 g
Malic acid	2.00 g
Azosemide	1.00 g
Polyethylene glycol (macrogol 400)	500.00 g
Methionine	10.00 g
Edetic acid disodium salt (Titriplex III)	0.50 g
Water for injection ad	5.00l

2.5 l of water for injection are placed in a vessel of sufficient size which is provided with a stirrer and macrogol is dissolved therein while stirring and under N_2 gasification. The carvedilol is suspended in the mixture while stirring vigorously and dissolved by the addition of malic acid and the azosemide. The pH value is adjusted to 4.4 to 4.8 with 1N NaOH, methionine and Titriplex III are dissolved and the mixture is made up with water for injection to the final volume.

The solution is filtered over a 0.2 µm membrane filter or filter candle, filled into ampoules on a suitable filling machine under N_2 gasification and sterilized for 20 minutes at 121°C in a steam sterilizer.

Claims:

1. A ready-to-inject injection solution containing carvedilol or its pharmacologically harmless salts as the active substance, said injection solution containing a physiologically compatible buffer having a pH value of 7.2 to 4.0, a water-soluble organic solvent, an antioxidant and an agent which binds heavy metal ions.

2. An injection solution according to claim 1, wherein the carvedilol concentration is 1 to 5 mg/ml.

3. An injection solution according to claim 1 or 2, wherein the buffer is a sodium, potassium or ammonium salt of a weak acid and/or a loop diuretic or its sodium or potassium salt.

4. An injection solution according to claim 3, wherein the loop diuretic is torasemide, azosemide or furosemide.

5. An injection solution according to any one of claims 1 to 4, which has a buffer capacity of up to 5 mVal/l and a titration basicity from 10 mmol/l to 0.05 mmol/l.

6. An injection solution according to claim 5, wherein the buffer capacity is up to 1 mVal/l and the titration basicity is from 1.0 mmol/l to 0.05 mmol/l.

7. An injection solution according to any one of claims 1 to 6, wherein the water-soluble organic solvent is polyethylene glycol, trimethylene glycol or ethanol.

8. An injection solution according to claim 7, wherein the water-soluble organic solvent is polyethylene glycol.

9. An injection solution according to claim 8, wherein the polyethylene glycol has a molecular weight of 100 to 1,500.

10. An injection solution according to claim 8, wherein the polyethylene glycol has a molecular weight of 200 to 600.

11. An injection solution according to any one of claims 1 to 10, wherein the antioxidant is an inorganic or organic sulphur compound or ascorbate.

12. An injection solution according to claim 11, wherein the organic sulphur compound is methionine or sodium disuphide.

13. An injection solution according to any one of claims 1 to 12, wherein the agent which binds heavy metal ions is a complex former.

14. An injection solution according to claim 13, wherein the complex former is EDTA or its disodium salt.

15. An injection solution according to any one of claims 1 to 14, wherein additives are present for adjusting isotonicity.

16. A process for the production of a ready-to-inject injection solution in accordance with claims 1 to 15, which process comprises suspending the active substance in the organic solvent and a part of the required water and dissolving it by the addition of the appropriate amount of buffer substance, if desired adjusting the solution to the desired pH value of 4.0 to 7.4 by the addition of alkali, adding the antioxidant and the agent which binds heavy metal ions in dissolved form and, if desired, adding other additives for adjustment of the isotonicity and making up the solution to the final volume with water.

17. The invention as described above.

INTERNATIONAL SEARCH REPORT

Interr ›nal Application No
PCT/EP 99/04974

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/40 A61K47/00

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 308 862 A (OHLSTEIN ELIOT H) 3 May 1994 (1994-05-03) * see col. 7, lines 6-34; col. 8, lines 30-35 * ---	1-17
A	WO 96 24348 A (BOEHRINGER MANNHEIM PHARM CORP ;LUKAS LASKEY MARY ANN (US); RUFFOL) 15 August 1996 (1996-08-15) *see page 6, line 26 - page 7, line 16 * --- -/--	1-17

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"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

Date of the actual completion of the international search	Date of mailing of the international search report
7 October 1999	12/11/1999

Name and mailing address of the ISA	Authorized officer
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	Isert, B

2

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/04974

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	DASGUPTA P ET AL: "CAN INTRAVENOUS BETA-BLOCKADE PREDICT LONG-TERM HEMODYNAMIC BENEFIT IN CHRONIC CONGESTIVE HEART FAILURE SECONDARY TO ISCHEMIC HEART DISEASE? A COMPARISON OF INTRAVENOUS WITH ORAL CARVEDILOL" JOURNAL OF CARDIOVASCULAR PHARMACOLOGY, vol. 19, no. SUPPL. 01, 1 January 1992 (1992-01-01), pages S62-S67, XP000578581 ISSN: 0160-2446 *see the abstract; p. S63 "Study design" * ---	1-17
A	EP 0 004 920 A (BOEHRINGER MANNHEIM GMBH) 31 October 1979 (1979-10-31) cited in the application * page 8, lines 8-16 * -----	1-17

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 99/04974

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5308862 A	03-05-1994	AU 679462 B	03-07-1997
		AU 5092393 A	26-09-1994
		CA 2157488 A	15-09-1994
		CZ 9502282 A	12-06-1996
		EP 0746315 A	11-12-1996
		HU 72888 A,B	28-06-1996
		JP 8508013 T	27-08-1996
		NO 953480 A	03-11-1995
		WO 9420097 A	15-09-1994
		US 5643939 A	01-07-1997
		US 5453436 A	26-09-1995
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
		FI 973255 A	07-08-1997
		HU 9900773 A	28-07-1999
		JP 10513463 T	22-12-1998
		NO 973667 A	08-08-1997
		PL 321737 A	22-12-1997
		US 5902821 A	11-05-1999
EP 0004920 A	31-10-1979	DE 2815926 A	18-10-1979
		AT 375639 B	27-08-1984
		AU 522975 B	08-07-1982
		AU 4582079 A	18-10-1979
		BG 61419 B	31-07-1997
		CA 1129416 A	10-08-1982
		CS 227007 B	16-04-1984
		CS 9104200 A	15-04-1992
		CS 227047 B	16-04-1984
		DD 143607 A	03-09-1980
		DK 141979 A,B,	14-10-1979
		ES 479396 A	16-04-1980
		FI 791142 A,B,	14-10-1979
		HK 2385 A	18-01-1985
		JP 1023462 B	02-05-1989
		JP 1545837 C	28-02-1990
		JP 54157558 A	12-12-1979
		JP 63258416 A	25-10-1988
		LT 2628 R	25-04-1994
		LU 88320 A	04-05-1994
		LV 5234 A	10-10-1993
		MX 9203380 A	01-09-1992
		SG 52284 G	29-03-1985
		US 4503067 A	05-03-1985
		ZA 7901732 A	28-05-1980