

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No 03-048164

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

PCT FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **533**

DE FECHA **31 DE OCTUBRE DE 2003** EL TERMINO HABIL SEÑALADO POR

LA LEY EXPIRA EL **30 DE ENERO DEL 2004**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____ NO X _____

Bogotá D.C, SEPTIEMBRE DE 2007



US005985915A

United States Patent [19][11] **Patent Number:** **5,985,915****Frangin et al.**[45] **Date of Patent:** **Nov. 16, 1999****[54] USE OF ANTIARRHYTHMIC COMPOUNDS
IN THE PREVENTION OF POST-
INFARCTION MORTALITY****[73] Inventors:** **Gerald Frangin**, Montpellier; **Alain Munoz**, Fontaine-les-Dijons, both of France**[73] Assignee:** **Sanofi**, Paris, France**[21] Appl. No.:** **08/819,863****[22] Filed:** **Mar. 17, 1997****[30] Foreign Application Priority Data**

Mar. 18, 1996 [FR] France 96 03357

[51] Int. Cl.⁶ A61K 31/34**[52] U.S. Cl. 514/469****[58] Field of Search 514/469****[56] References Cited****U.S. PATENT DOCUMENTS**

5,223,510 6/1993 Gubin et al. 514/299

FOREIGN PATENT DOCUMENTS

WO9509625-

A1 4/1995 WIPO .

OTHER PUBLICATIONS

Am. J. Cardiol., vol. 72, No. 16, 1993, pp. 70f-74f, XP000607627.

Ann. Inter. Med., vol. 122, No. 9, 1995, pp. 689-700, XP000607576.

Chew et al.—J. Cardiovasc. Pharmacoc. vol. 4 (6), 1028-36 (Abstract), 1982.

Patterson et al.—Circulation (Med. Sch., Univ. of Mich.) vol. 68 (4) 857-64 (Abstract), 1983.

Seidl et al.—Ptsch. Med. Wochenschr. vol. 120 (18), 656-60, Germany (Abstract), 1995.

Primary Examiner—Raymond Henley, III*Attorney, Agent, or Firm*—Jacobson, Price, Holman & Stern, PLLC**[57] ABSTRACT**

The subject of the invention is a method for reducing mortality of cardiac origin in patients having a reduced left ventricular function after myocardial infarction, without rhythm disorders requiring an antiarrhythmic treatment, consisting in administering to said patients an effective amount of one or more active ingredients selected from benzofuran derivatives with antiarrhythmic activity and pharmaceutically acceptable salts thereof in combination with one or more pharmaceutically acceptable vehicles.

30 Claims, 4 Drawing Sheets

5,985,915

5

benzoyl]-5-methylsulphonamidobenzo-furan or dronedarone and its pharmaceutically acceptable salts which are described in U.S. Pat. No. 5,223,510.

However, amiodarone and its pharmaceutically acceptable salts which are described in U.S. Pat. No. 3,248,410 is generally preferred as benzofuran derivative with antiarrhythmic activity.

In fact "amiodarone" is understood to mean, in the context of the present invention, 2-n-butyl-3-(4-diethylaminoethoxybenzoyl)benzofuran in basic form or in the form of inclusion complexes in cyclodextrins, their ethers or their esters.

The use of the active metabolites of the benzofuran derivatives with antiarrhythmic activity referred to above, also forms part of the present invention. As an example of such metabolites, there may be mentioned 2-n-butyl-3-(4-ethylaminoethoxybenzoyl)-benzofuran or N-desethylamiodarone and its pharmaceutically acceptable salts as described in patent FR 2,550,091 and 2-n-butyl-3-[4-(3-n-butylamino-propoxy)benzoyl]-5-methylsulphonamidobenzo-furan or N-desbutyldronedarone and its pharmaceutically acceptable salts described in U.S. Pat. No. 5,223,510.

Likewise, the term "mortality of cardiac origin" covers, within the framework of the invention, the mortality due to any cardiac causes (any deaths except those due to a noncardiac cause) in particular, and more particularly, cardiac mortality of arrhythmic origin.

"Cardiac mortality of arrhythmic origin" in fact designates mortality, sudden or otherwise, due to any arrhythmic cause, that is to say either death occurring within an hour or less than an hour following the appearance of new symptoms in the absence of worsened left ventricular insufficiency or of shock, or death, without a witness, of an apparently stable patient, or fatal ventricular fibrillation ("nonresuscitated").

The term "cardiac mortality of arrhythmic origin" also covers, within the framework of the invention, nonfatal cardiac arrests ("resuscitated" after defibrillation), that is to say the nonfatal arrhythmic events causing a cardiac arrest.

Furthermore, the expression "cardiac mortality of arrhythmic origin" also includes more specifically "sudden cardiac mortality of arrhythmic origin" or "sudden mortality of arrhythmic origin" or "sudden death", namely death occurring within an hour or less than an hour following the appearance of new symptoms in the absence of worsened left ventricular insufficiency or the fortuitous death of a patient without symptoms or with stable cardiovascular symptoms which occurred without a witness and within 24 hours of knowing of this event.

It may also be specified that the expression "patient having a reduced left ventricular function following myocardial infarction, without rhythm disorders requiring an antiarrhythmic treatment" means a patient who, with a reduced left ventricular function after myocardial infarction, may possibly have asymptomatic rhythm disorders, that is to say without pathological significance but no rhythm disorders requiring an antiarrhythmic treatment.

Finally, "reduced left ventricular function" is understood to mean essentially a deficient left ventricular function reflected by an ejection fraction $\leq 40\%$.

As will be described in greater detail later, it has been observed during a trial involving several hundreds of patients, that amiodarone, preferably in the form of its hydrochloride, administered daily after the acute phase of myocardial infarction, does not cause any detrimental effect over a period of 24 months.

6

In addition, it has been found that this antiarrhythmic agent tends to prevent mortality of cardiac origin in some specific cases, for example in patients with an ejection fraction greater than 30% and less than or equal to 40% in a first infarction period, that is to say patients who have not had one or more previous infarctions.

Likewise, it has been possible to demonstrate that amiodarone hydrochloride can significantly prevent over a period of at least 2 years, cardiac mortality of arrhythmic origin, sudden or otherwise, comprising or not comprising nonfatal cardiac arrests, since it has been possible to record a reduction of 28 to 30% in this type of mortality at 2 years.

Moreover, it has been found that amiodarone hydrochloride may also reduce, quite significantly, sudden mortality of arrhythmic origin or sudden death over a period of 24 months (37% reduction at 24 months).

This prophylactic effect, which has also been observed in patients with an ejection fraction greater than 30% and less than or equal to 40%, even proved more marked in patients with a considerably reduced left ventricular ejection fraction, that is to say $< 30\%$.

For their use in therapy, the benzofuran derivatives with antiarrhythmic activity according to the invention are generally introduced into pharmaceutical compositions.

These pharmaceutical compositions may be provided in any form appropriate for their administration in human therapy, especially for administration by the oral, sublingual, nasal, inhaled, parenteral, topical, transdermal or rectal route.

Generally, the oral or parenteral route, preferably the oral route, is used. As regards the administerable unit, it may take the form, for example, of a tablet, scored or otherwise, a sugar-coated tablet, a capsule, a gelatine capsule, a powder, a suspension or a syrup for oral administration, of a suppository for rectal administration, of a solution or suspension for parenteral administration or of a device commonly called "patch" for transdermal administration.

The pharmaceutical compositions according to the invention may advantageously comprise, per administerable unit, from 50 to 600 mg of active ingredient, especially from 150 to 250 mg for oral administration, from 10 to 250 mg of active ingredient for parenteral administration or from 50 to 200 mg of active ingredient for rectal administration.

Pharmaceutical compositions may especially be prepared containing amiodarone, dronedarone or one of their pharmaceutically acceptable salts in an amount of 50 to 500 mg for oral administration, more particularly oral compositions containing from 150 to 250 mg of amiodarone or one of its pharmaceutically acceptable salts or from 50 to 150 mg of dronedarone or one of its pharmaceutically acceptable salts.

According to the route of administration chosen, the pharmaceutical compositions in question will be conventionally prepared by combining the active ingredient, such as amiodarone or dronedarone or one of their pharmaceutically acceptable salts, with an appropriate pharmaceutical excipient or vehicle, it being possible for the latter to consist, for example, of at least one ingredient selected from the following substances:

lactose, starches, talc, magnesium stearate, polyvinylpyrrolidone, alginic acid, colloidal silica, polysorbate, mannitol, sodium dihydrogen phosphate, distilled water, benzyl alcohol or sweetening agents.

For the preparation of an oral pharmaceutical composition, the active ingredient may for example be mixed with the pharmaceutical excipients or vehicles selected and then subjected to a dry or wet granulation.

According to the nature of the excipient used, it is possible, if necessary, to obtain, simply by mixing, a powder

United States Patent [19]

Bodor

[11] Patent Number: 4,983,586

[45] Date of Patent: Jan. 8, 1991

[54] PHARMACEUTICAL FORMULATIONS FOR PARENTERAL USE

[75] Inventor: Nicholas S. Bodor, Gainesville, Fla.

[73] Assignee: University of Florida, Gainesville, Fla.

[21] Appl. No.: 174,945

[22] Filed: Mar. 29, 1988

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 139,755, Dec. 30, 1987.

[51] Int. Cl.⁵ A61K 9/18; C08B 37/16

[52] U.S. Cl. 514/58; 536/103; 514/777

[58] Field of Search 536/103; 514/58, 777

[56] References Cited

U.S. PATENT DOCUMENTS

3,459,731	8/1969	Gramera et al.	260/209
4,024,223	5/1977	Noda et al.	514/58
4,228,160	10/1980	Szejtli et al.	558/344
4,232,009	11/1980	Hayashi et al.	514/58
4,351,846	9/1982	Matsumoto et al.	514/530
4,352,793	10/1982	Yamahira et al.	514/58
4,383,992	5/1983	Lipari	514/174
4,407,795	10/1983	Nicolau	514/58
4,424,209	1/1984	Tuttle	514/58
4,425,336	1/1984	Tuttle	514/58
4,438,106	3/1984	Wagu et al.	514/58
4,474,811	10/1984	Matsuda et al.	514/570
4,478,995	10/1984	Shinoda et al.	536/46
4,479,932	10/1984	Bodor	424/9
4,479,944	10/1984	Hayashi et al.	514/58
4,479,966	10/1984	Hayashi et al.	514/58
4,497,803	2/1985	Harada et al.	514/450
4,499,085	2/1985	Masuda	514/58
4,518,588	5/1985	Szejtli et al.	514/58
4,524,068	6/1985	Szejtli et al.	514/58
4,540,564	9/1985	Bodor	424/9
4,555,504	11/1985	Jones	514/26
4,565,807	1/1986	Uekama et al.	514/58
4,575,548	3/1986	Ueda et al.	536/46
4,596,795	6/1986	Pitha	514/58
4,598,070	7/1986	Ohwaki et al.	514/58
4,599,327	7/1986	Nogradi et al.	514/58

4,603,123	7/1986	Chiesi et al.	514/58
4,608,366	8/1986	Hasegawa et al.	514/58
4,617,298	10/1986	Bodor et al.	514/176
4,623,641	11/1986	Szejtli et al.	514/58
4,659,696	4/1987	Hirai et al.	514/15
4,663,316	5/1987	Ninger et al.	514/99
4,675,395	6/1987	Fukazawa et al.	536/103
4,727,064	2/1988	Pitha	514/58
4,727,079	2/1988	Bodor	514/307
4,728,509	3/1988	Shimizu et al.	424/81
4,728,510	3/1988	Shibanai et al.	424/94.5
4,751,095	6/1988	Karl et al.	426/548
4,824,850	4/1989	Bodor	514/270
4,829,070	5/1989	Bodor	514/307
4,834,985	5/1989	Elger et al.	424/488
4,888,427	12/1989	Bodor	546/316

FOREIGN PATENT DOCUMENTS

59-104556	6/1984	Japan
8303968	11/1983	PCT Int'l Appl.
8502767	7/1985	PCT Int'l Appl.
8503937	9/1985	PCT Int'l Appl.

OTHER PUBLICATIONS

Pitha et al., in *Controlled Drug Delivery*, ed. S. D. Bruck, vol. I, CRC Press, Boca Raton, Florida, 125-148 (1983).

(List continued on next page.)

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[57] ABSTRACT

Aqueous parenteral solutions of drugs which are insoluble or only sparingly soluble in water and/or which are unstable in water, combined with hydroxypropyl- β -cyclodextrin, provide a means for alleviating problems associated with drug precipitation at the injection site and/or in the lungs or other organs following parenteral administration.

41 Claims, 2 Drawing Sheets

Quat-Level in Brain

