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PATENTE DE INVENCION

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54. TITULO

USO DE UN DERIVADO DE AMINA CICLICA ESPECIFICO O DE SUS

SALES FARMACEUTICAMENTE ACEPTABLES PARA TRATAR I PREVENIR

LA INSUFICIENCIA CARDIACA

51. CLASIFICACION INTERNACIONAL

71. SOLICITANTE

BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG.

DOMICILIO

Ingelheim am Rhein, República Federal de Alemania.

74. APODERADO

EMILIO FERRERO

C.C. 438,019 de Usaquén.

22. BOGOTA, D.C.,


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PCT
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1
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☐ Patente de Modelo de Utilidad.

☐ Capítulo I.

☒ Capítulo II.

2
**SOLICITANTE
(71)**

 Nombre: **BOEHRINGER INGELHEIM
PHARMA GMBH & CO. KG**
 sociedad constituida y existente bajo las
 leyes de la República Federal de Alemania

 Dirección: 55216 Ingelheim am Rhein,
 República Federal de Alemania

 Domicilio: Ingelheim am Rhein,
 República Federal de Alemania

IDENTIFICACIÓN

 C.C. ☐ NIT ☐

 C.E. ☐ Otro ☐

Cual _____

Número _____

3
**REPRESENTANTE
APODERADO**

 Nombre: **EMILIO FERRERO**
 Dirección: **Carrera 4ª. No. 72-35**
 Teléfono: **347 38 11**
 Fax: **211 86 50**
 E-mail: **clientes@camyp.com.**
 Domicilio: **Bogotá, Colombia.**
IDENTIFICACIÓN

 C.C. ☒ NIT ☐

 C.E. ☐ Otro ☐

Cual _____

 Número **438.019** T.P **31.929**
4
**INVENTOR (ES)
(72)**

 1. **Brian GUTH**
 Kirchensteige 12,
 88447 Warthausen,
 República Federal de Alemania

 3. **Randolph SEIDLER**
 4 Lester Road,
 Sandy Hook, Connecticut 06482,
 Estados Unidos de América

 2. **Juergen DAEMMGEN**
 Hattenburg Mittelbucherstrasse 14,
 88416 Ochsenhausen,
 República Federal de Alemania

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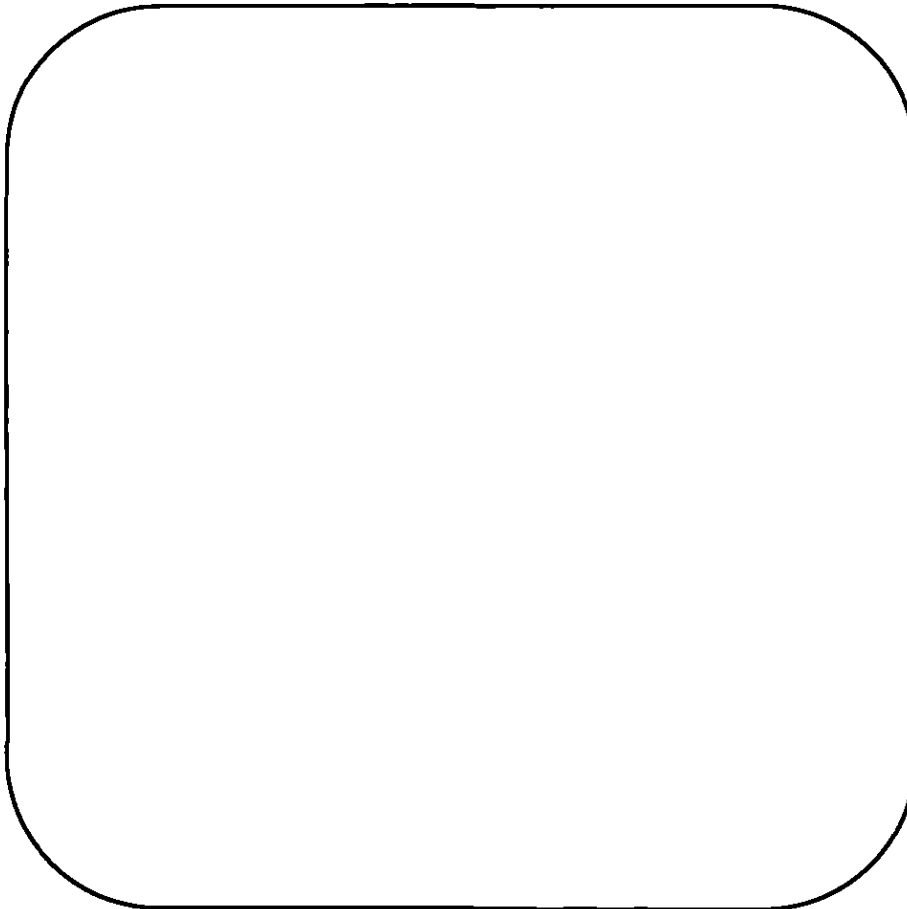
10

An xos:

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por \$ 443.000.00.
- ☐ Comprobante de pago por reivindicación de prioridad.
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso.
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- ☐ Declaraciones.
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
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- ☐ Arte final 12x12
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☒ Otros: REIVINDICACIONES MODIFICADAS DURANTE LA FASE INTERNACIONAL (ART. 19 DEL PCT)
REIVINDICACIONES MODIFICADAS PARA INICIAR LA FASE NACIONAL

11

FIGURA CARACTERÍSTICA



12

Solicito la concesión de la patente,

NOMBRE: EMILIO FERREROFIRMA: 
C.C. 438.019 de Usaquén T.P. 31.929

PRP

179

promuevan. Y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir los hechos del proceso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

admit the facts of the case, desist, cancel, receive, resign, and ratify done by representatives without a power of attorney.

Dado y firmado hoy/Given and signed this 21st day of March
en/in Ingelheim
por/by _____

Firma

Signature

BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG
ppa.


Dr. Heinz-Gerd KLÄS
Head of Patent Department


Dr. Michael KOMPTER
Principal Officer

COMO NOTARIO SEXTO DEL CIRCULO
DE BOGOTA, HAGO CONSTAR QUE LA
FOTOCOPIA CONCORDA CON EL ORIGINAL
QUE HE TENIDO A LA VISTA
15 FEB 2005
JUAN MANUEL ESPINOSA MEDINA
NOTARIO

AUTENTICACION NOTARIAL (SOCIEDAD)

El infrascrito Notario Certifica: Que la firma que antecede de

1. Heinz-Gerd Kläs

2. Michael Kompter

es auténtica; que el signatario desempeña actualmente el cargo

de Representante

de la compañía Boehringer Ingelheim Pharma

GmbH & Co. KG

sociedad que actualmente existe y está organizada de acuerdo a

las leyes de Alemania

que la dirección de la compañía es 55216 Ingelheim

am Rhein Binger Straße 173

y que el signatario tiene facultad para otorgar este documento.

Todos los hechos anteriores le constan por haber examinado los documentos respectivos y de todo da fe.

Dado y firmado en Ingelheim am Rhein

21 MARZO 2003

NOTARIAL AUTHENTICATION (COMPANY)

The undersigned Notary certifies: That the preceding signature

of 1.Mr.Dr.Heinz-Gerd Kläs and

2.Mr.Dr.Michael Kompter

is authentic, that the signatory currently acts in the position of

procurists

of the company Boehringer Ingelheim Pharma

GmbH & Co. KG

a company currently existing and organized under the laws of

Germany

that the address is 55216 Ingelheim am Rhein

Binger Straße 173

and that the signatory has the power to grant this document.

The Notary Public is aware and attests to the above facts upon examination of the corresponding documents.

Given and signed in Ingelheim am Rhein

On the 21th day of March 2003

Notary Public
(Signature-seal)



Apostille

(Convention de La Haye du 5 octobre 1961)

1. Land Bundesrepublik Deutschland

Diese öffentliche Urkunde

2. ist unterschrieben von

Alfred Fuchs

3. in seiner Eigenschaft als Notar

4. sie ist versehen mit dem Dienstsiegel

des Alfred Fuchs - Notar in Ingelheim am Rhein

Bestätigt

Mainz, den 24.03.03

5. in Mainz 6. am 24.03.03

7. durch den Präsidenten des Landgerichts

8. unter Nr. 269/2003

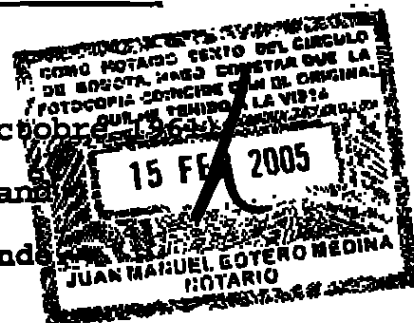
9. Stempel/Siegel 10. Unterschrift

In Vertretung:

Justizsekretärin



Dr. Harald Bing
(Dr. Harald Bing)
Vizepräsident



KOSTENRECHNUNG:

Gebühr für die

Erteilung der

Legalisation

Wert: EUR 20.000,00

JVKostO v.26.7.57

i.V.m. § 45 KostO

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TRADUCCION OFICIAL No. 9468

de un documento escrito en Alemán, efectuada por Luz Arriaga de Herber, resolución del Ministerio de Justicia 599 del 6 de marzo 1978.-

Traducción de los sellos y autenticaciones en Alemán que aparecen en el documento de representación y poder, escrito en español e inglés, por medio del cual la firma Boehringer Ingelheim Pharma GmbH & Co. KG, domiciliada en D-55216 Ingelheim am Rhein, Alemania, otorga poder a EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa 23555 y GERMAN CAVELIER, tpa. 832, domiciliados en la Carrera 4 No. 72-35, Bogotá, Colombia. Dado y firmado el 21 de marzo 2003 en Ingelheim am Rhein por los señores Dr. Heinz-Gerd KLÄS y Dr. Michael KOMPTER, representantes legales de la mencionada firma.

Sigue autenticación notarial en español e inglés de los antecedentes por el notario de Ingelheim am Rhein, Alfred Fuchs, el 21 de marzo 2003, bajo el No. 571/2003.

COSTAS:

Derechos de legalización

Valor: EUROS 20.000,--

LUZ A. ARRIAGA DE HERBER
TRADUCCION OFICIAL
15 FEB 2005
JUAN MANUEL BUTERQUE
NOTARIO

JVKostO del 26.7.57 en combinación con Art. 45 KostO

Derechos: EUROS 18,00

Mainz, 24.03.03

Fdo.: ilegible,

Secretaria de justicia

APOSTILLA

(Convention de La Haye du 5 octobre 1961)

1. País: República Federal de Alemania

Este documento público

2. Ha sido firmado por el notario Alfred Fuchs

3. Actuando en calidad de notario

4. Lleva el sello oficial del notario de Ingelheim am Rhein,
Alfred Fuchs

Certificado

5. en Mainz

6. el 24.03.03

7. por el Presidente del Tribunal Regional

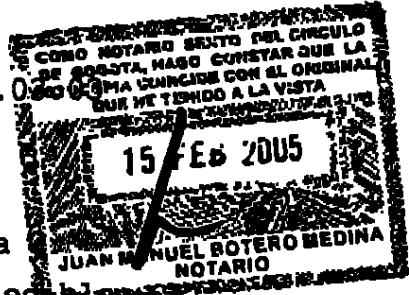
8. bajo el No 269/2003 /

9. Sello

10. Firma

Tribunal Regional de Mainz

Fdo.: ilegible
(Dr. Harald Binz)
Vicepresidente



ES TRADUCCION FIEL Y COMPLETA, de la cual se deja copia en los
archivos de estas oficinas para su confrontación.

Bogotá, 7 de abril 2003

[Handwritten signature]
LIZ AL...
DE UL...
NOTARIO

COMO NOTARIO SEXTO DEL CIRCULO DE SANTAFE DE BOGOTA. HAGO CONSTAR QUE LA(S) FIRMA(S) DE

Luz Arriaga de
Herber

CONCORDA CON LA FIRMA REGISTRADA POR (L. 11108) EN ESTA NOTARIA

SANTAFE DE BOGOTA, 09 ABR 2002



NO SE ASUME RESPONSABILIDAD DEL TEXTO

2003 MAR - 10 1:08

JEFE DE VOUCHERS

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Luz Arriaga de Herber

CUYA FIRMA ES: FELICIELA

DOCUMENTO D. SERPILA

LAS FUNCIONES INCLUIDAS

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA CONCURRE CON EL ORIGINAL QUE ME FOMDO A LA VISTA

15 FEB 2005

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BOEHRINGER INGELHEIM PHARMA GMBH
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(72) Inventors; and

(75) Inventors/Applicants (*for US only*): GUTH, Brian
[DE/DE]; Kirchensteige 12, 88447 Warthausen (DE).
DAEMMGEN, Juergen [DE/DE]; Hattenburg Mittel-
buchenstrasse 1/2, 88416 Ochsenhausen (DE). SEIDLER,

*For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: USE OF A SPECIFIC CYCLIC AMINE DERIVATIVE OR THE PHARMACEUTICALLY ACCEPTABLE SALTS
THEREOF FOR THE TREATMENT OR PREVENTION OF HEART FAILURE

(57) Abstract: The present invention provides the use in a pharmaceutical composition of a specific cyclic amine derivative, or its
pharmaceutically acceptable salts, for the treatment or prevention of heart failure of any aetiology.

WO 2004/011006 A1

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**USE OF CILOBRADINE OR THE PHARMACEUTICALLY ACCEPTABLE SALTS THEREOF FOR THE
TREATMENT OR PREVENTION OF HEART FAILURE**

FIELD OF THE INVENTION

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The present invention relates to the novel use of a cyclic amine derivative, namely cilobradine, or the pharmaceutically acceptable salts thereof, for the treatment or prevention of heart failure of any aetiology.

15

BACKGROUND OF THE INVENTION

Heart failure is a major world-wide public health problem and is the only cardiac disorder that is increasing in incidence. In the United States alone, 5 million patients suffer from heart failure, with a new diagnosis made in 0.5 million patients per year. Despite advances in therapy over the last decade, the annual number of hospitalisations has increased from 550 000 to 900 000 as a primary diagnosis, and from 1.7 to 2.6 million as a primary or secondary diagnosis (J. Am. Pharm. Assoc., vol. 41(5), pp. 672-681, 2001). Unless treated, heart failure may lead to death. Hence, new approaches are warranted to treat or prevent heart failure.

Although the terminology heart failure seems to be the most accepted terminology for describing this cardiac disorder, various further equivalent terminologies can be found in the scientific, patent or medical literature as, for example, cardiac failure, insufficient cardiac output, cardiac insufficiency, cardiac collapse and cardiac syncope.

Furthermore, though heart failure is invariably a chronic cardiac disorder, often with an insidious onset, heart failure may be present acutely or be punctuated by episodes of acute deterioration, so called "decompensated" heart failure. To describe these conditions also related to heart failure, further terminologies will commonly be found in the scientific, patent or medical literature such as, for example, chronic heart failure, acute heart failure, heart decompensation, cardiac decompensation and cardiac decompensation.

Lastly, as will be explained in the foregoing, as heart failure can be caused by a dysfunctioning of the heart reflected by various clinical presentations and sometimes subjected to further complications, further terminologies related to heart failure will also commonly be found in the scientific, patent or medical literature such as, for example, myocardial failure, myocardial insufficiency, heart muscle insufficiency, cardiac muscle insufficiency, heart muscle weakness, cardiac muscle weakness, systolic or left ventricular heart failure, diastolic heart failure, left or right sided heart failure, biventricular heart failure and congestive heart failure.

Hence, a distinction can be made between the systolic or diastolic origin of the dysfunctioning. Commonly, heart failure is a consequence of a progressive deterioration of myocardial contractile function, named systolic or left ventricular dysfunction. However, diastolic dysfunction is becoming increasingly

recognised as an important cause of heart failure too. This occurs when the heart chambers are unable to expand sufficiently during diastole (period of heart relaxation in which the chambers fill with blood) and hence blood volume in the ventricles is inadequate. Whether systolic and/or diastolic dysfunction is the basis of heart failure, cardiac output is diminished. When additionally there is "damming" back of blood in the venous system, congestion may ensue in the lungs (pulmonary oedema) and/or in the abdomen or peripheries (peripheral oedema). When both occur, the terminology congestive heart failure is often used.

10

In other respects, the distinction between left and right sided heart failure can be applied to reflect the clinical presentation (i.e. pulmonary oedema indicative of left sided heart failure, whereas the principal symptom of right sided heart failure is fluid retention in the peripheries) or to denote the underlying cause.

15

Right sided heart failure is most commonly a consequence of left sided heart failure, although diseases of the lung (such as chronic obstructive pulmonary disease), the right ventricle (e.g. right ventricular infarction) or the vasculature (primary or secondary pulmonary hypertension, the latter due to conditions such as pulmonary embolism for example), may result in predominate right sided heart failure.

20

According to the International Classification of Functioning, Disability and Health, lastly published by the World Health Organization on 15 November 2001 (ISBN 91 4 1545429) and accepted by 191 countries during the 54th World Health Assembly (Resolution WHA 54.21), heart failure occurs when the heart function of pumping the blood in adequate or required amounts and pressure throughout the body is impaired.

25

As cardiac output is normally 5 litres/minute, although this can increase five fold with heavy exercise, in essence, heart failure occurs when the heart is unable to meet this demand.

- 5 As heart failure manifests itself in a variety of ways, at the time of this patent application, the treatment or prevention of heart failure comprises a combination of typical medications. These medications are based upon the principles of promoting fluid excretion to lessen oedema and volume overload (e.g. various types of diuretics), vasodilatory drugs to reduce preload (i.e. atrial pressures)
10 and/or afterload (i.e. pressure against which the heart has to beat), and inotropic drugs to increase contractility.

Vasodilatory drugs available at this time include Angiotensin Converting Enzyme (ACE) inhibitors, Angiotensin II Receptor blockers (ARBs) and nitrate
15 venodilators. Inotropic drugs are usually administered only in acute situations. Although cardiac glycosides such as digoxin are sometimes prescribed for their inotropic properties, their use is more common in heart failure patients when atrial arrhythmias co-exist.

- 20 Recently, beta-blockers, which were once thought to be contra-indicated in heart failure due to their negative inotropic (decreased contractility) property, have been shown to be effective in the treatment of heart failure. Meta-analyses of randomised controlled trials have shown that, in addition to established background therapy of ACE inhibitors and diuretics with or without digoxin, a
25 reduction of all cause mortality and cardiovascular morbidity is conferred by beta-blockers such as carvedilol, metoprolol or bisoprolol (Brophy J. M. et al., Ann. Intern. Med. 2001, Vol. 134, pp. 550-560; Lechat P. et al., Circ. 1998, pp. 1184-1191; Heldenreich P. A. et al., J. Am. Coll. Cardiol., 1997, Vol. 30, pp 27-

12

34).

As heart failure progresses, heart failure treatment is also usually not limited to one single therapy. Hence, add-on therapy use is disclosed for carvedilol, for example, in WO 96/24348, for decreasing the mortality of patients suffering from congestive heart failure. WO 96/40258 discloses a combination therapy comprising an angiotensin II antagonist and spironolactone, an aldosterone receptor antagonist, for the treatment of hypertension, congestive heart disease, cirrhosis and ascites. WO 00/02543 discloses a combination therapy comprising an angiotensin II antagonist (valsartan) and a calcium channel blocker (amlodipine or verapamil) for the treatment of several heart diseases, amongst which acute and chronic congestive heart diseases are cited.

However, as with all therapies, there are constraints to their use. For example, beta-blockers may be contra-indicated in patients with concomitant diseases such as asthma, peripheral vascular disease and decompensated heart failure. Certain drug classes may not be tolerated due to unwanted side effects, e.g. cough with ACE inhibitors, fatigue, dizziness or impotence in association with beta-blockers, and hyponatraemia with diuretics. Furthermore, a slow and careful titration period may be required upon drug initiation, as with beta-blockers, where if not performed, the initial negative effects on the heart's pumping action (negative inotropy) may result in drug intolerance and deterioration in heart failure status.

Hence, to echo the statement set out at the beginning of this section, despite the advances made by therapies established at this time, there is still a need to reduce the unacceptable burden of heart failure and new additional

approaches to treatment and prevention of disease progression should be sought.

In searching for new therapies for heart failure, the underlying pathophysiology of the failing heart needs to be considered. It has long been observed in the failing heart that heart rate and contractility are initially increased in order to maintain cardiac performance. In the long term, this response is ultimately damaging. It is, for example, acknowledged that increased heart rate is a risk factor for mortality and morbidity with adverse consequences on vascular function, atherogenesis, myocardial ischaemia, myocardial energetics and left ventricular function. Chronic tachyarrhythmias are a cause of reversible cardiomyopathy in humans and rapid atrial pacing is established as an animal model of cardiomyopathy. In chronic heart failure, excess adrenergic stimulation signals adverse biological responses (including increased heart rate) via β_1 , β_2 and α_2 receptors in the myocardium.

In the failing heart, maintenance of adequate ventricular contraction is sought, but occurs at the expense of oxygen and energy consumption by the myocardium. Heart rate influences such energy demand, with increased heart rate requiring greater expenditure of energy. Thus, greater energetic efficiency could potentially result if heart rate were lowered in heart failure patients.

It thus follows that drugs which have the ability to reduce heart rate may be of benefit in the treatment or prevention of heart failure. For the treatment of cardiac insufficiency, a term also used to denote heart failure, EP 0 471 388 (and its US counterpart US Patent 5,516,773) suggests the use of a specific group of compounds derived from the benzazepine basic chemical structure, and more specifically the compound named zatebradine [1-(7,8-dimethoxy-

1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-3-yl)-3-[N-methyl-N-(2-(3,4-dimethoxy-phenyl)-ethyl)-propane].

These benzazepine derivatives were firstly described in EP 0 065 229, as well
5 as their ability to reduce heart rate (bradycardic effect) by acting directly on the sinoatrial node, and their ability to reduce the oxygen requirement of the heart.

Zatebradine is also known from WO 01/78699 for the treatment and induction
of the regression of idiopathic hypertrophic cardiomyopathy (HCM), ischemic
10 cardiomyopathy and valvular hypertrophic heart diseases.

The effects of the bradycardic agent zatebradine have been studied in a small
number of patients with heart failure, also subject to no therapy or atrial
pacing, to induce a tachycardia (Shinke et al., Jpn. Circ. Journal, 1999, Vol.
15 63, pp. 957-964) or in comparison to the beta-blocker propranolol (Shinke et
al. Abstract Circ., 1997, Vol. 96, I-644).

In the former study, it was concluded by the authors that the oxygen saving
effect of the bradycardia due to zatebradine treatment could be beneficial for
20 the treatment of heart failure. In the latter study, the comparable heart rate
reduction observed with zatebradine and the beta-blocker had favourable
effects compared to pre-treatment. However, it should be noted that under
beta-blocker treatment overall cardiac efficiency was preserved, since the
energy saving benefits of heart rate reduction remedied the observed negative
25 effect on contractility. This, the authors proposed, might account for good
beta-blockers tolerance and possible efficacy in heart failure. Zatebradine
treatment however improved cardiac efficiency since heart rate reduction
occurred, but with no accompanying adverse effect on contractility.

It should be noted that these two studies are small and do not attempt to evaluate the benefits of chronic zatebradine administration on the haemodynamic or clinical manifestations of heart failure. Furthermore, the relationships between heart rate reduction, left ventricular function and prognosis in heart failure are complex. However, there is a scientific rationale that improved cardiac energetics secondary to heart rate reduction is an important concept in the treatment and prevention of the progression of heart failure due to systolic and/or diastolic dysfunction (Laperche et al., Heart 1999, Vol. 81, pp. 338-341).

Another specific group of compounds derived from a basic cyclic amine chemical structure, have been shown to also have valuable pharmacological bradycardic properties. These compounds, the process for their preparation and pharmaceutical compositions containing them are described in EP 0 224 784 and its US counterpart US Patent 5,175,157.

One of these cyclic amine derivatives, 3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one, and more particularly its S-(+) enantiomer named clobradine [(+)-3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)-piperidin-3-(S)-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one], is also known from WO 01/78699 for the treatment and induction of the regression of idiopathic hypertrophic cardiomyopathy (HCM), ischemic cardiomyopathy and valvular hypertrophic heart diseases.

However, these cyclic amine derivatives, and more specifically clobradine, have not been suggested for the treatment or prevention of heart failure.

Scientific studies performed with zatebradine and cilobradine in order to determine the mechanism of action of these bradycardic substances have shown that both zatebradine and cilobradine selectively block hyperpolarisation activated, cAMP-modulated cation current channels (HCN) in cardiac conductive tissue, channels responsible for the transmembrane current known as I_h . It is through blockade of this current that zatebradine and cilobradine are assumed to produce their specific bradycardic effect.

However, HCN channels are widely distributed in the nervous system, and in the eye they mediate the current known as I_h . The effect of zatebradine and cilobradine on the I_h channel has also been investigated (Neuroscience, Vol. 59(2), pp. 363-373, 1994 for zatebradine, and British Journal of Pharmacology, Vol. 125, pp. 741-750, 1998 for cilobradine). The results have suggested that although I_h can also be blocked by these compounds, the interaction with the channels is somewhat different for both tissues. Since I_h has been described in the different neurones of the visual signal processing system, the effect on I_h current has been suggested to be an explanation for the side-effects (visual disturbances) seen by patients treated with I_h blockers.

20

Further studies have been performed using electroretinogram (ERG) responses recorded from cat eyes and psychophysical measurements conducted on volunteer human subjects, in normal conditions and after administration of zatebradine (Archives Italiennes de Biologie, vol. 137, pp. 299-309, 1999, and Vision Research, vol. 39, pp. 1767-1774, 1999). The results of these studies have shown that zatebradine reduces the amplitude of the response to stimuli of frequency above 1 Hz, as shown by the ERG recordings. Furthermore, the measurement of the attenuation and phase

25

characteristics of the first harmonic constructed by plotting the response amplitude and the phase as a function of the temporal frequency of the stimulus in control conditions and after intravenous injection or oral administration of zatebradine have shown that the main effect of the I_h blocker
5 zatebradine is to decrease the response amplitude to stimuli in the frequency range of 2 to 15 Herz, by introducing a cut-off in the band-pass at about 2 Herz.

To confirm these assumptions, recent studies have been performed using
10 intraretinal and vitreal electroretinogram (ERG) recordings in dark-adapted intact cat retina (Visual Neuroscience, vol. 18(3), pp. 353-363, 2001). These studies compared the changes in the recovery phase following the a- and b-waves induced by an exposure with bright flashes of diffuse white light, after intraretinal injections of substances known to block the responses of bipolar
15 and horizontal cells, or substances known to block I_h . The authors of this study have concluded that blockers of I_h reduce the recovery phase following the a-wave induced by the light exposure.

20 SUMMARY OF THE INVENTION

From the results of the recently published scientific studies on the mechanism of action of bradycardic substances, which were discussed in the previous section, one would not expect an advantage of clobetradine over zatebradine in
25 the treatment of cardiac disorders such as heart failure.

However, as shall be discussed below, it has surprisingly been found that clobetradine presents an advantage over zatebradine not only in terms of its

pharmacologically longer duration of action and dose potency, but more importantly in its cardioselectivity, resulting in decreased or absent visual side effects when compared to therapeutic doses of zatebradine.

5 Hence, a first object of the present invention is that clobradine has intrinsically different pharmacological properties than zatebradine, which permit full cardiac ion channel blockade with absent or diminished retinal effects. This unexpected cardioselective property represents a clear advantage for clobradine over, for example, zatebradine, for the treatment of cardiac
10 disorders such as heart failure.

A further object of the present invention is that clobradine is effective for the treatment or prevention of heart failure of any aetiology and thus, is able to reduce the mortality and morbidity associated with heart failure of any
15 aetiology.

Thus, the present invention is directed to the use of clobradine, or its pharmaceutically acceptable salts, for the treatment or prevention of heart failure of any aetiology.

20

The present invention is also a method for the treatment or prevention of heart failure of any aetiology, by administration to a patient in need thereof of a pharmaceutical composition comprising clobradine, or its pharmaceutically acceptable salts, together with a pharmaceutically suitable carrier.

25

DESCRIPTION OF PREFERRED EMBODIMENTS

In accordance with one embodiment, the present invention provides for a novel use of the cyclic amine derivative (+)-3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)-piperidin-3-(S)-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one, named clobradine, or its pharmaceutically acceptable salts.

For the preparation of clobradine or the pharmaceutically acceptable salts of clobradine, reference is made to EP 0 224 794 and its US counterpart US Patent 5,175,157, which describes the chemical synthesis of these compounds.

In accordance with a further embodiment of the present invention, amongst the pharmaceutically acceptable salts of clobradine described in EP 0 224 794 and its US counterpart US Patent 5,175,157, the hydrochloride and hydrobromide salts of clobradine are preferred.

More particularly, the present invention is directed to the use of clobradine, or its pharmaceutically acceptable salts, for the preparation of a pharmaceutical composition for the treatment or prevention of heart failure of any aetiology.

In accordance with a further embodiment, the present invention is directed to the use of clobradine, or its pharmaceutically acceptable salts, for the preparation of a pharmaceutical composition for the prevention of heart failure of any aetiology.

In accordance with a further embodiment of the present invention, the treatment or prevention of heart failure may be assessed by the ability of the compound or pharmaceutical composition in accordance with the present

invention to reduce the mortality and morbidity associated with heart failure of any aetiology.

5 In accordance with a further embodiment of the present invention, the treatment or prevention of heart failure also comprises the treatment or prevention of cardiac insufficiency, cardiac failure, heart insufficiency, myocardial failure, myocardial insufficiency, heart muscle insufficiency, cardiac muscle insufficiency, insufficient cardiac output, heart muscle weakness, cardiac muscle weakness, cardiac collapse, cardiac syncope, chronic heart
10 failure, acute heart failure, heart decompensation, cardiac decompensation, cardiac decompensation, diastolic heart failure, right sided heart failure, systolic heart failure, left ventricular heart failure, left sided heart failure, biventricular heart failure and congestive heart failure.

15 In accordance with a further embodiment of the present invention, heart failure of any aetiology means heart failure diagnosed as a consequence or complication of any other condition, disease or disorder such as, for example, systolic dysfunction, diastolic dysfunction, ischaemic heart diseases, including myocardial infarction, right ventricular infarction and chronic ischaemia,
20 coronary heart diseases, hypertension, primary pulmonary hypertension, secondary pulmonary hypertension, pulmonary embolism, pulmonary arterial stenosis, chronic obstructive pulmonary disease, restrictive cardiomyopathies, dilated cardiomyopathies due to infectious, toxic, metabolic, familial or unknown reasons, myocarditis, congenital anomalies, tachycardias and
25 ventricular hypertrophy secondary to genetic or valvular disorders such as tricuspid valve insufficiency, mitral and/or aortic valve disorders, heart infarcts, thyroid diseases and anaemia.

21

In accordance with a further embodiment, for the treatment or prevention of heart failure, a combination of clobradine, or its pharmaceutically acceptable salts, with other substances such as, for example, diuretics, cardiac glycosides, ACE (Angiotensin Converting Enzyme) Inhibitors, ARBs (Angiotensin Receptor Blockers), vasodilators, beta blockers and inotropes, present in the same pharmaceutical composition, or given as separate therapies (so-called adjunctive therapy), is also within the scope of the present invention.

10 In accordance with a further embodiment of the present invention, the pharmaceutical composition for use in accordance with the present invention, comprising clobradine or its pharmaceutically acceptable salts, alone or in combination with other heart failure therapies including ACE inhibitors, ARBs, diuretics or cardiac glycosides, may be administered to patients in any medically acceptable manner.

In accordance with a further embodiment of the present invention, the pharmaceutical composition for use in accordance with the present invention, comprising clobradine or its pharmaceutically acceptable salts, may be formulated as liquid formulation or lyophilised powder for oral or parenteral administration. Powders may be reconstituted by addition of a suitable diluent or other pharmaceutically acceptable carrier prior to use. The liquid formulation is generally an aqueous solution. Such formulation is especially suitable for oral administration, but may also be used for parenteral administration or contained in a metered dose inhaler or nebulizer for insufflation. It may be desirable to add excipients such as polyvinylpyrrolidone or hydroxycellulose to the composition.

In accordance with a further embodiment of the present invention, the liquid formulation may be administered directly per orally or filled into a soft capsule.

- 5 Alternatively, the ingredients may be encapsulated, tableted or prepared in a syrup for oral administration. Pharmaceutically acceptable solid or liquid carriers may be added to enhance or stabilise the composition, or to facilitate the preparation of the composition. The carrier may also include a sustained release material.

10

In accordance with a further embodiment of the present invention, the pharmaceutical compositions are prepared following the conventional techniques of pharmacy involving milling, mixing, granulating, and compressing, when necessary, for tablet forms, or milling, mixing and filling for capsule forms.

15

- For the preparation of pharmaceutical compositions comprising clobradine or its pharmaceutically acceptable salts, reference is made in particular to EP 0 224 794 and its US counterpart US Patent 5,175,157 and to WO 01/78699, which describe examples of injectable, oral liquid, tablet, capsule and suppository formulations of clobradine or its pharmaceutically acceptable salts.

20

- In accordance with a further embodiment of the present invention, the preferred galenical formulation is a tablet or liquid drinking solution, although capsule, suppository and injectable formulations of the active substance clobradine or its pharmaceutically acceptable salts are also comprised within the scope of the present invention.

25

In accordance with a further embodiment of the present invention, the pharmaceutical composition comprising the active compound clobradine or its pharmaceutically acceptable salts can be administered to animals as well as
5 humans.

In accordance with a further embodiment of the present invention, the pharmaceutical composition comprising the active compound clobradine or its pharmaceutically acceptable salts is preferably administered following a single
10 or multiple stage daily application scheme.

In accordance with a further embodiment of the present invention, when administered for the treatment or prevention of heart failure, preferably a dose of 0.01 to 20 mg/kg body weight of the active substance clobradine or its
15 pharmaceutically acceptable salts is used, and this in one or more applications per day. Within this range, the following dose ranges are further preferred: 0.05 to 5 mg/kg body weight, 0.1 to 2.5 mg/kg body weight, 0.1 to 1 mg/kg body weight, and 0.1 to 0.75 mg/kg body weight.

20 The invention will now be described in more detail with reference to the following experiments.

As already mentioned above, previous studies (published in Archives Italiennes de Biologie, vol. 137, pp. 299-309, 1999, and Vision Research, vol.
25 39, pp. 1767-1774, 1999) have established an experimental animal model to evaluate the side-effects (visual disturbances) seen by patients treated with bradycardic agents, such as zatebradine. The content of these references,

and more particularly the experimental parts described therein, are herein incorporated by reference.

These studies were based on a measurement of the electroretinogram (ERG) responses recorded from cat eyes, in normal conditions and after administration of zatebradine.

In the following experiment, the same experiment was performed using cilobradine, and the results compared to the results obtained with zatebradine.

10

In order to compare the visual side-effect of both compounds in conditions in which the drugs are pharmacologically the most effective in these experiments, as for example in the reduction of heart rate, a dose of 0.75 mg/kg body weight was chosen for cilobradine and a dose of 2.5 mg/kg body weight was chosen for zatebradine. This selection of the dose is based on the result shown in Figure 1, wherein the reduction of heart rate is plotted against the applied dose of the drug (open circles: zatebradine; filled circles: cilobradine). As can be seen from Figure 1, at a dose of 2.5 mg/kg body weight, a reduction of about 44% of the heart rate is obtained with zatebradine (maximum effect), and at a dose of 0.75 mg/kg body weight, a reduction of about 75% of the heart rate is obtained with cilobradine (also maximum effect). Therefore, by choosing these doses, it can already be assumed that the pharmacological effect on heart rate of cilobradine is better than the pharmacological effect of zatebradine.

25

In a similar experiment than the experiment performed by Gargini et al. (published in Vision Research, vol. 39, pp. 1767-1774, 1999), the attenuation and phase characteristics of the ERG response to sinusoidally modulated

luminances was evaluated by plotting the amplitude of the response to the light stimulus as a function of the temporal frequency of the light stimulus. The result of this experiment is shown in Figure 2, wherein the open circles are the control responses (no active substance injected), the filled circles are the responses 15 minutes after treatment with a dose of zatebradine of 2.5 mg/kg body weight (i.v. injection), and the triangles are the responses measured 5 hours after the injection of zatebradine.

The results confirm the results already published by Gargini et al. (Vision Research, vol. 39, pp.1767-1774, 1999) that, at this dose, zatebradine reduces the amplitude of the response to stimuli of frequency above 1 Hz and shift the corresponding phase lags, as shown by the ERG recordings. The measurements performed after 5 hours confirm that the visual response is back to normal after 5 hours, and that the experiment is non-destructive for the system.

Figure 3 shows the results of the same experiment performed after injection of 0.75 mg/kg body weight of clobradine, in the same conditions. As is clear from the result, no visual effect can be detected with clobradine when injected in a fully heart rate reduction effective dose.

We conclude from these results that a dose of clobradine which produces a saturation effect on the heart rate has negligible consequences on the visual response. This evidences the advantage of clobradine over zatebradine to produce a pharmacological effect with less side-effect, and thus its superiority for the treatment of heart failure.

26

A further similar experiment was performed in order to compare the visual side-effect of cilobradine and zatebradine in conditions where the drugs are pharmacologically effective in reducing heart rate. The aim of this experiment was to compare the visual side-effect of both drugs in another experimental animal model, namely on the retinal system of the rat. Furthermore, the aim of this experiment was also to compare the visual side-effect of both drugs in acute and in chronic (over two weeks) drug treatment conditions.

The principle of this experiment is again the same as the principle of the experiment performed by Gargini et al. and published in Vision research, vol. 39, pp. 1767-1774, 1999).

Hence, this experiment was based on a measurement of the electroretinogram (ERG) responses recorded from anesthetized pigmented rats as a function of the temporal frequency of an applied oscillating light stimulus. The results of the experiment are visualized by plotting the measurement of the first amplitude of the Fourier transform of the ERG as a function of the applied stimulus frequency (oscillating light stimulus of high luminance and contrast).

Figures 4 to 7 show the results of the experiment in different treatment conditions.

Figure 4 shows the results of the experiment in control conditions (squares and circles) and in acute treatment conditions with three different doses of cilobradine (triangles: 0.3 mg cilobradine /kg body weight; inverted triangles: 1 mg cilobradine /kg body weight; diamonds: 3 mg cilobradine /kg body weight). The ERG measurements were made 30 minutes after injection of the drug. The measured heart rate frequency was:

Control	400 beats per min.
Cilobradine treatment 0.3 mg/kg	364 beats per min.
Cilobradine treatment 1 mg/kg	316 beats per min.
Cilobradine treatment 3 mg/kg	270 beats per min.

5

Figure 5 shows the results of the experiment in control condition (squares and circles) and in acute treatment condition with a single dose of zatebradine of 3 mg /kg body weight (circles). The ERG measurement was made 30 minutes after injection of the drug. The measured heart rate frequency was:

10

Control	428 beats per min.
Zatebradine treatment 3 mg/kg	333 beats per min.

Figure 6 shows the results of the experiment in control condition (squares) and in chronic treatment condition with a single dose of cilobradine of 1 mg /kg body weight given per day during 2 weeks (circles). The ERG measurement was made after the 2 weeks treatment. The measured heart rate frequency was:

15

Control	400 beats per min.
Cilobradine treatment 1 mg/kg	260 beats per min.

20

Figure 7 shows the results of the experiment in control conditions (circles) and in chronic treatment conditions with a double dose of zatebradine of 3 mg /kg body weight given per day during 2 weeks (squares). The ERG measurement was made after the 2 weeks treatment. The measured heart rate frequency was:

25

Control	350 beats per min.
Cilobradine treatment 1 mg/kg	285 beats per min.

From this experiment, it can be concluded that in acute treatment (results of Figures 4 and 5), at doses for which both drugs are effective in reducing the heart rate (as confirmed by the values of the measured heart rate frequency),
5 no effect on the ERG can be detected with clobradine, whereas a reduction of the amplitude of the response to stimuli of frequency above 1 Hz and a shift of the corresponding phase lags is observed with zatebradine.

Furthermore, the same conclusions can be made from the results obtained
10 with chronic treatment over two weeks, as can be seen when comparing the results of Figures 6 and 7.

This experiment performed with rats confirms the results previously observed in cats that a dose of clobradine effective for reducing the heart rate has
15 negligible consequences on the visual response. This also demonstrates again the advantage of clobradine over zatebradine to produce a pharmacological effect with less side-effect, and thus its superiority for the treatment of heart failure.

20 This experiment further demonstrates that clobradine is effective in reducing heart rate without visual side-effects, and thus its suitability in the acute treatment as well as in the chronic treatment of heart failure.

The invention will now also be described in more detail with reference to the
25 following examples of pharmaceutical dosage formulations.

Hence, pharmaceutical formulations for medical use in humans have been prepared containing between 0,10 and 5 mg of active substance. More

specifically, oral tablet formulations to be used as single or multiple dose in a daily application scheme, and containing 0,25 mg, 0,5 mg, 1 mg or 2 mg active substance, have been prepared as described in the following formulation examples of film coated tablets.

5

	Example 1	Example 2	Example 3	Example 4
	0,25mg Dosis mg/Film Coated Tablet	0,5mg Dosis mg/Film Coated Tablet	1mg Dosis mg/Film Coated Tablet	2mg Dosis mg/Film Coated Tablet
Core:				
Cilobradine	0,27	0,54	1,08	2,16
Lactose Monohydrat (Tablettose)	56,42	56,15	82,28	164,56
Microcrystalline Cellulose, Type 101	27,45	27,45	40,38	80,76
Na- Carboxymethylcellulose (Ac-Di-Sol)	0,43	0,43	0,63	1,26
Magnesiumstearate, (vegetal origin)	0,43	0,43	0,63	1,26
Weight of Tablet Core:	85,00	85,00	125,00	250,00
Coating:				
Hypromellose (Methocel E5 Premium)	1,50	1,50	2,00	3,00
Macrogol 400	0,15	0,15	0,20	0,30
Titaniumdioxide	0,75	0,75	1,00	1,50
Talkum	0,60	0,60	0,80	1,20
Weight of Film Coated Tablet:	88,00	88,00	128,00	256,00

These tablets may be used for the treatment or prevention of heart failure as defined in the present invention.

CLAIMS

5 1. Use of clobradine or a pharmaceutically acceptable salt thereof
for the preparation of a pharmaceutical composition for the treatment or
prevention of heart failure.

 2. Use in accordance with claim 1, wherein the pharmaceutical
10 composition is for the prevention of heart failure.

 3. Use in accordance with claim 1 or 2, wherein the galenical
formulation of the pharmaceutical composition is a tablet, a drinking solution, a
capsule, a suppository or an injectable formulation.

15 4. Use in accordance with any one of claims 1 to 3, wherein the
galenical formulation of the pharmaceutical composition is a tablet.

 5. Use in accordance with any one of claims 1 to 3, wherein the
20 galenical formulation of the pharmaceutical composition is a drinking solution.

 6. Use in accordance with any one of claims 1 to 5, wherein the
pharmaceutical composition is administered following a single or multiple
stage daily application scheme.

25 7. Use in accordance with claim 6, wherein the administered dose
of clobradine or its pharmaceutically acceptable salt is comprised between
0.01 and 20 mg/kg body weight.

8. Use in accordance with claim 6, wherein the administered dose of cilobradine or its pharmaceutically acceptable salt is comprised between 0.05 and 5 mg/kg body weight.

5

9. Use in accordance with claim 6, wherein the administered dose of cilobradine or its pharmaceutically acceptable salt is comprised between 0.1 and 2.5 mg/kg body weight.

10

10. Use in accordance with claim 6, wherein the administered dose of cilobradine or its pharmaceutically acceptable salt is comprised between 0.1 and 1 mg/kg body weight.

15

11. Use in accordance with claim 6, wherein the administered dose of cilobradine or its pharmaceutically acceptable salt is comprised between 0.1 and 0.75 mg/kg body weight.

20

12. Use in accordance with any one of claims 1 to 11, wherein the treatment or prevention of heart failure is performed in combination with other therapeutic agents for the treatment or prevention of heart failure, such as diuretics, cardiac glycosides, ACE inhibitors, ARBs, vasodilators, beta blockers or inotropes.

25

13. A method for the treatment or prevention of heart failure, which comprises the administration to a patient in need thereof of a pharmaceutical composition comprising cilobradine or a pharmaceutically acceptable salt thereof, together with a pharmaceutically suitable carrier.

AMENDED CLAIMS

[received by the International Bureau on 26 November 2003 (26.11.03);
original claims 1 – 13 replaced by new claims 1 - 17]

CLAIMS

1. Use of clobradine or a pharmaceutically acceptable salt thereof
5 for the preparation of a pharmaceutical composition for the treatment or prevention of heart failure.

2. Use in accordance with claim 1, wherein the pharmaceutical composition is for the prevention of heart failure.

10

3. Use in accordance with claim 1, wherein the pharmaceutical composition is for the treatment or prevention of diastolic heart failure.

4. Use in accordance with claim 3, wherein the pharmaceutical
15 composition is for the prevention of diastolic heart failure.

5. Use in accordance with claim 1, wherein the pharmaceutical composition is for the treatment or prevention of systolic heart failure.

20 6. Use in accordance with claim 5, wherein the pharmaceutical composition is for the prevention of systolic heart failure.

7. Use in accordance with any one of claims 1 to 6, wherein the galenical formulation of the pharmaceutical composition is a tablet, a drinking
25 solution, a capsule, a suppository or an injectable formulation.

8. Use in accordance with any one of claims 1 to 7, wherein the galenical formulation of the pharmaceutical composition is a tablet.

AMENDED SHEET (ARTICLE 19)

35

9. Use in accordance with any one of claims 1 to 7, wherein the galenical formulation of the pharmaceutical composition is a drinking solution.
10. Use in accordance with any one of claims 1 to 9, wherein the pharmaceutical composition is to be administered following a single or multiple stage daily application scheme.
11. Use in accordance with claim 10, wherein clobrodine or its pharmaceutically acceptable salt is to be administered between 0.01 and 20 mg/kg body weight.
12. Use in accordance with claim 10, wherein clobrodine or its pharmaceutically acceptable salt is to be administered between 0.05 and 5 mg/kg body weight.
13. Use in accordance with claim 10, wherein clobrodine or its pharmaceutically acceptable salt is to be administered between 0.1 and 2.5 mg/kg body weight.
14. Use in accordance with claim 10, wherein clobrodine or its pharmaceutically acceptable salt is to be administered between 0.1 and 1 mg/kg body weight.
15. Use in accordance with claim 10, wherein clobrodine or its pharmaceutically acceptable salt is to be administered between 0.1 and 0.75 mg/kg body weight.
16. Use in accordance with any one of claims 1 to 15, wherein the treatment or prevention of heart failure is performed in combination with other

AMENDED SHEET (ARTICLE 19)

therapeutic agents for the treatment or prevention of heart failure, such as diuretics, cardiac glycosides, ACE inhibitors, ARBs, vasodilators, beta blockers or inotropes.

- 5 17. A method for the treatment or prevention of heart failure, which comprises the administration to a patient in need thereof of a pharmaceutical composition comprising clobradine or a pharmaceutically acceptable salt thereof, together with a pharmaceutically suitable carrier.

AMENDED SHEET (ARTICLE 19)

Fig. 1

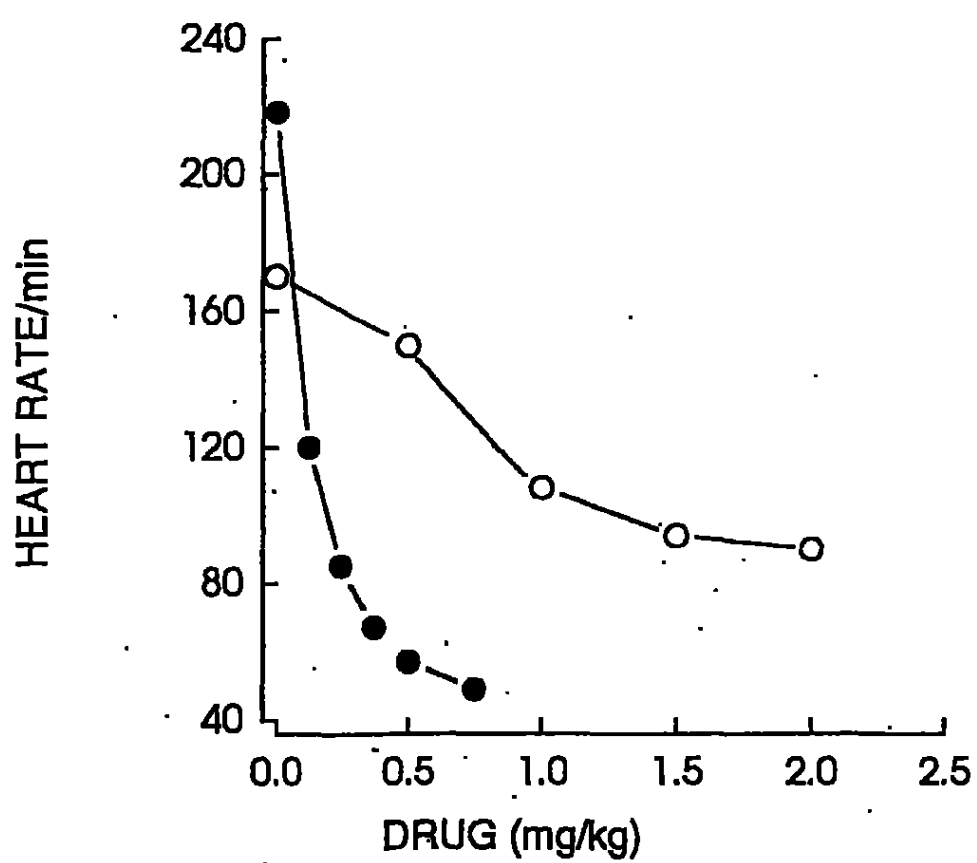


Fig. 2

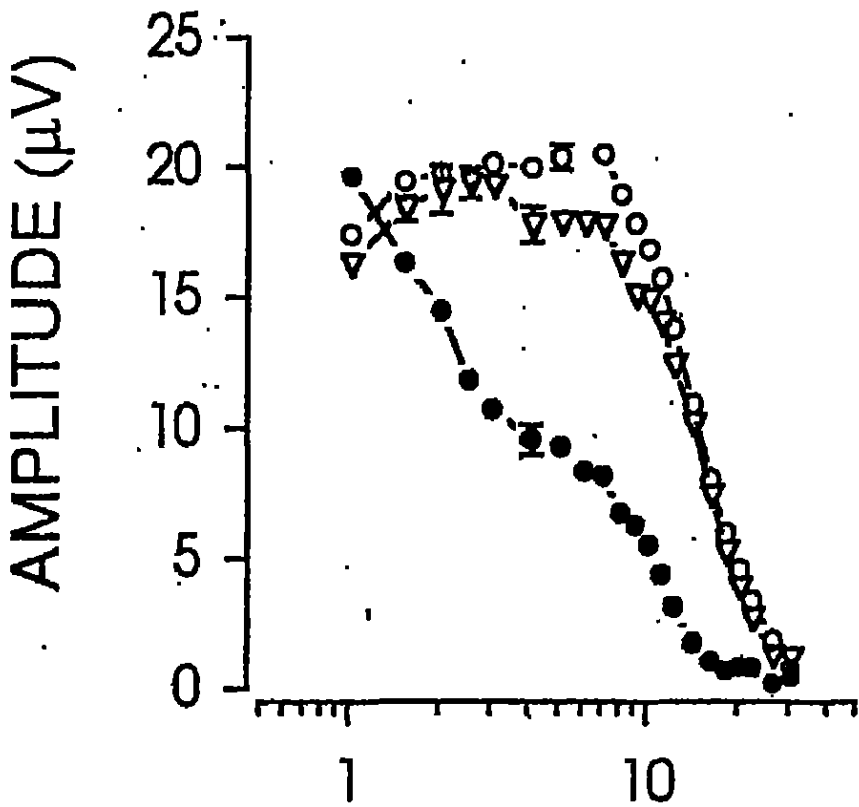
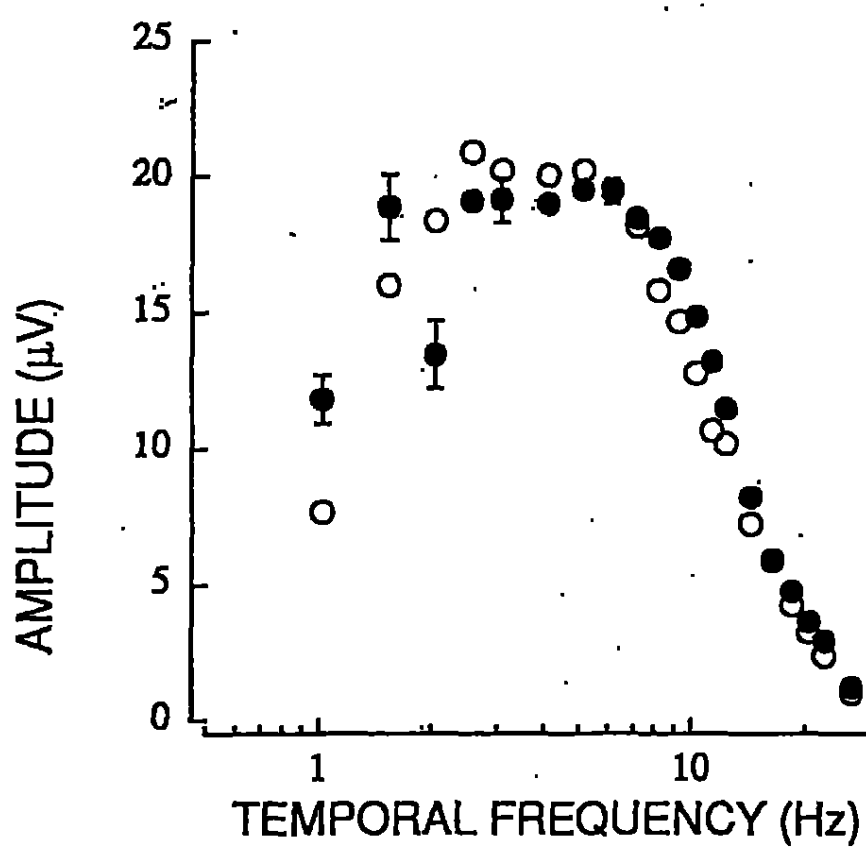


Fig. 3



VO

Fig. 4

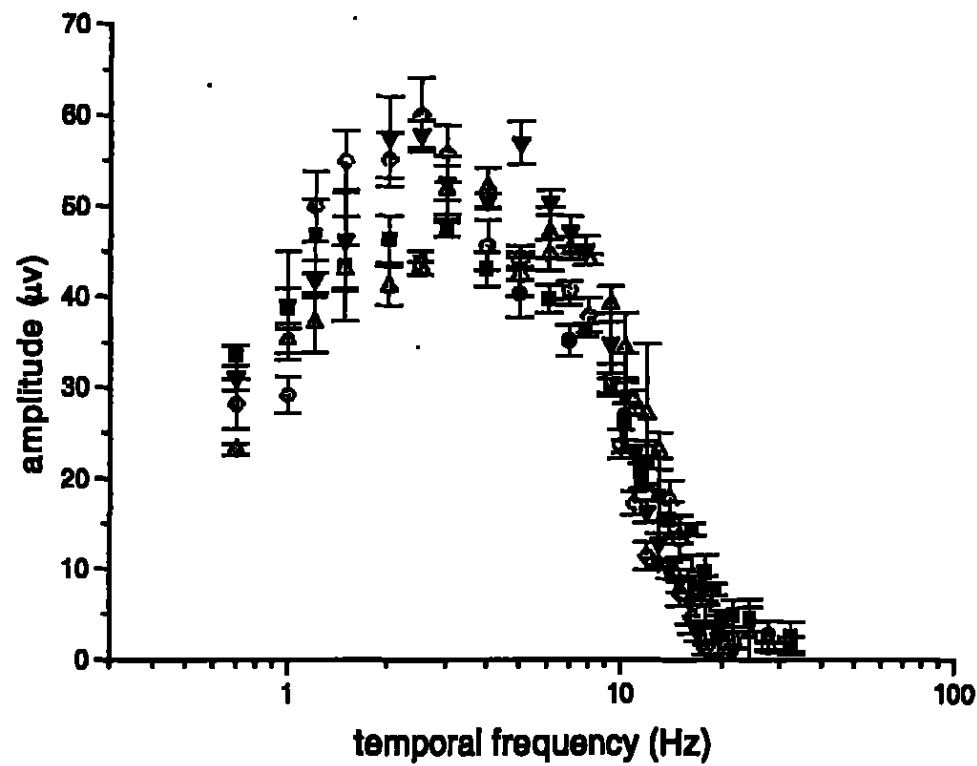


Fig. 5

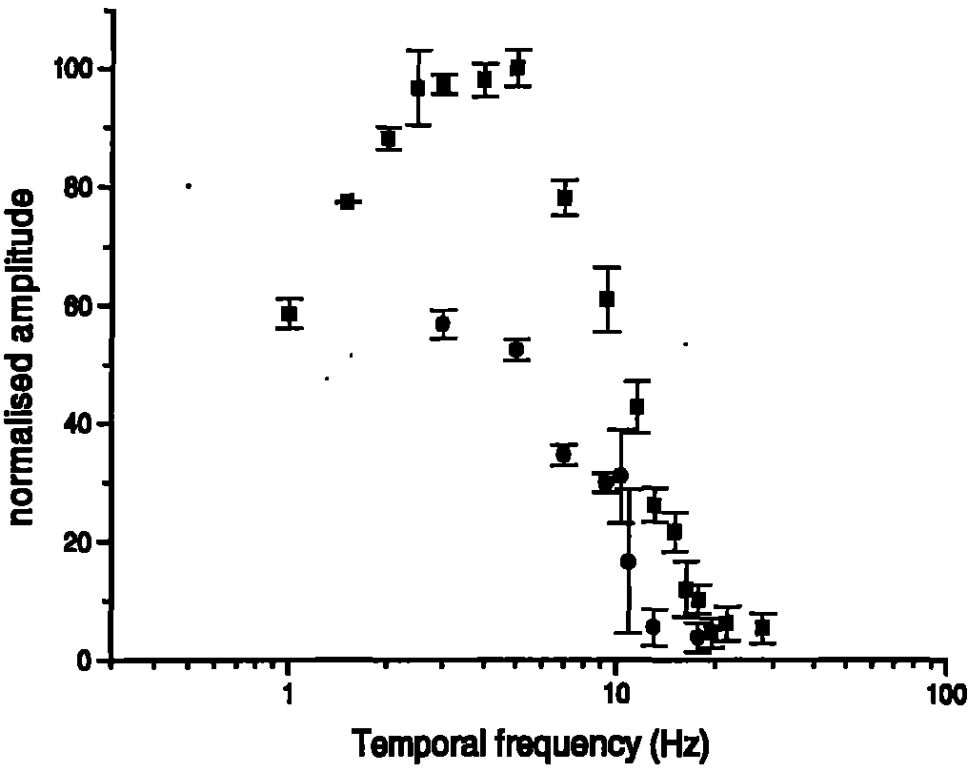


Fig. 6

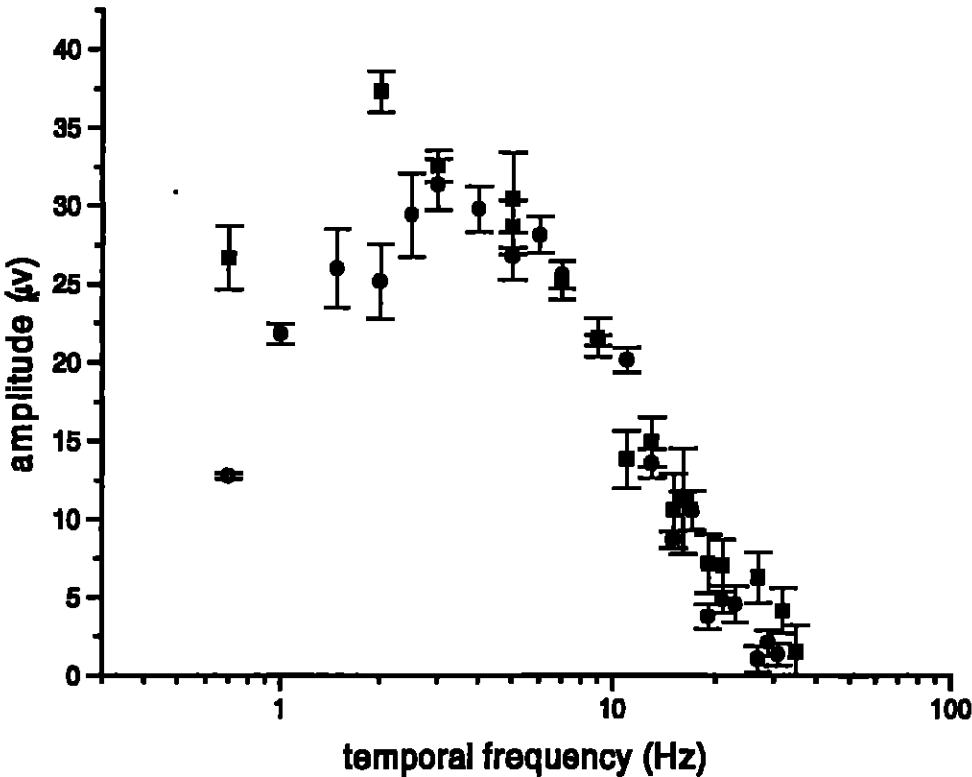
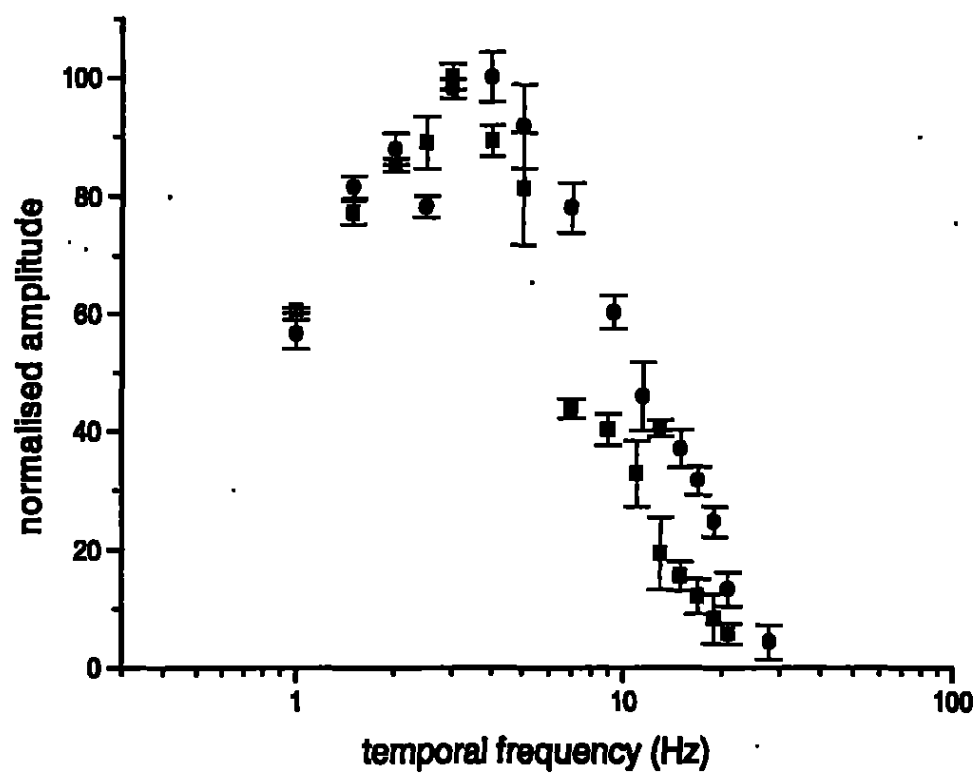


Fig. 7



INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/07929

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/55 A61P9/04

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 A61P

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)

EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS, MEDLINE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 78699 A (BOEHRINGER INGELHEIM PHARMA ;GUTH BRIAN (DE); DAEMMGEN JUERGEN (DE) 25 October 2001 (2001-10-25) cited in the application	1-13
Y	page 2, line 20 -page 4, line 17	1-13
Y	EP 0 471 388 A (THOMAE GMBH DR K) 19 February 1992 (1992-02-19) cited in the application	1-13
	page 2, line 54 -page 3, line 27 claims 1-5	
Y	EP 0 224 794 A (THOMAE GMBH DR K) 10 June 1987 (1987-06-10) cited in the application	1-13
	page 15, line 31 -page 16, line 18	
	-/-	



Further documents are listed in the continuation of box C.



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 relating 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

1 October 2003

Date of mailing of the international search report

09/10/2003

Name and mailing address of the ISA

European Patent Office, P.O. 5818 Patenplatz 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 21 851 apo nl,
Fax: (+31-70) 340-2016

Authorized officer

Herrera, S

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 03/07929

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SHINKE T ET AL: "BENEFICIAL EFFECTS OF HEART RATE REDUCTION ON CARDIAC MECHANICS AND ENERGETICS IN PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION" JAPANESE CIRCULATION JOURNAL, KYOTO, JP, vol. 63, no. 12, December 1999 (1999-12), pages 957-964, XP001041863 ISSN: 0047-1828 abstract	1-13
A	EP 0 330 052 A (THOMAE GMBH DR K) 30 August 1989 (1989-08-30) claims 1-10	1-13

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

Continuation of Box I.1

Although claim 13 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.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/07929

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:
see FURTHER INFORMATION sheet PCT/ISA/210
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:
3. ☐ Claims Nos.: —
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 8.4(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:

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.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/07929

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/07929

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0330052	A	30-08-1989	DE 3805635 A1	07-09-1989
			AT 98488 T	15-01-1994
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			EP 0330052 A2	30-08-1989
			JP 1254627 A	11-10-1989

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) Case 1/1370

Box No. I TITLE OF INVENTION USE OF A SPECIFIC CYCLIC AMINE DERIVATIVE OR THE PHARMACEUTICALLY ACCEPTABLE SALTS THEREOF FOR THE TREATMENT OR PREVENTION OF HEART FAILURE	
Box No. II APPLICANT ☐ This person is also inventor	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) Boehringer Ingelheim Pharma GmbH & Co. KG	Telephone No. 07351-54-4390 Facsimile No. 07351-54-4377 Teleprinter No. Applicant's registration No. with the Office
State (that is, country) of nationality: DE	State (that is, country) of residence: DE
This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) GUTH, Brian Kirchensteige 12 D-88447 Warthausen	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (if this check-box is marked, do not fill in below.) Applicant's registration No. with the Office
State (that is, country) of nationality: DE	State (that is, country) of residence: DE
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.	
Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE	
The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☐ agent ☐ common representative	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)	Telephone No. Facsimile No. Teleprinter No. Agent's registration No. with the Office
☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.	

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S) <i>If none of the following sub-boxes is used, this sheet should not be included in the request.</i>	
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i> DAEMMGEN, Juergen Hattenburg Mittelbacherstrasse 1/2 D-88416 Ochsenhausen	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State (that is, country) of nationality: DE	State (that is, country) of residence: DE
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i> SEIDLER, Randolph 314 Avalon Lake Dr. Danbury, CT 06810 USA	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State (that is, country) of nationality: DE	State (that is, country) of residence: US
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i> 	This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State (that is, country) of nationality:	State (that is, country) of residence:
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i> 	This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State (that is, country) of nationality:	State (that is, country) of residence:
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.	

Box No. V DESIGNATION OF STATES

Mark the applicable check-boxes below; at least one must be marked.

The following designations are hereby made under Rule 4.9(a):

Regional Patent

- ☒ **AP** ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZM Zambia, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT (*if other kind of protection or treatment desired, specify on dotted line*)
- ☒ **EA** Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ **EP** European Patent: AT Austria, BE Belgium, BG Bulgaria, CH & LI Switzerland and Liechtenstein, CY Cyprus, CZ Czech Republic, DE Germany, DK Denmark, EE Estonia, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, HU Hungary, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, RO Romania, SE Sweden, SI Slovenia, SK Slovakia, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ **OA** OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GQ Equatorial Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (*if other kind of protection or treatment desired, specify on dotted line*)

National Patent (*if other kind of protection or treatment desired, specify on dotted line*):

- | | | |
|---|--|---|
| ☒ AE United Arab Emirates | ☒ HR Croatia | ☒ OM Oman |
| ☒ AG Antigua and Barbuda | ☒ HU Hungary | ☒ PG Papua New Guinea |
| ☒ AL Albania | ☒ ID Indonesia | ☒ PH Philippines |
| ☒ AM Armenia | ☒ IL Israel | ☒ PL Poland |
| ☒ AT Austria | ☒ IN India | ☒ PT Portugal |
| ☒ AU Australia | ☒ IS Iceland | ☒ RO Romania |
| ☒ AZ Azerbaijan | ☒ JP Japan | ☒ RU Russian Federation |
| ☒ BA Bosnia and Herzegovina | ☒ KE Kenya | |
| ☒ BB Barbados | ☒ KG Kyrgyzstan | ☒ SC Seychelles |
| ☒ BG Bulgaria | ☒ KP Democratic People's Republic of Korea | ☒ SD Sudan |
| ☒ BR Brazil | ☒ KR Republic of Korea | ☒ SE Sweden |
| ☒ BY Belarus | ☒ KZ Kazakhstan | ☒ SG Singapore |
| ☒ BZ Belize | ☒ LC Saint Lucia | ☒ SK Slovakia |
| ☒ CA Canada | ☒ LK Sri Lanka | ☒ SL Sierra Leone |
| ☒ CH & LI Switzerland and Liechtenstein | ☒ LR Liberia | ☒ SY Syrian Arab Republic |
| ☒ CN China | ☒ LS Lesotho | ☒ TJ Tajikistan |
| ☒ CO Colombia | ☒ LT Lithuania | ☒ TM Turkmenistan |
| ☒ CR Costa Rica | ☒ LU Luxembourg | ☒ TN Tunisia |
| ☒ CU Cuba | ☒ LV Latvia | ☒ TR Turkey |
| ☒ CZ Czech Republic | ☒ MA Morocco | ☒ TT Trinidad and Tobago |
| ☒ DE Germany | ☒ MD Republic of Moldova | |
| ☒ DK Denmark | ☒ MG Madagascar | ☒ TZ United Republic of Tanzania |
| ☒ DM Dominica | ☒ MK The former Yugoslav Republic of Macedonia | ☒ UA Ukraine |
| ☒ DZ Algeria | ☒ MN Mongolia | ☒ UG Uganda |
| ☒ EC Ecuador | ☒ MW Malawi | ☒ US United States of America |
| ☒ EE Estonia | ☒ MX Mexico | |
| ☒ ES Spain | ☒ MZ Mozambique | ☒ UZ Uzbekistan |
| ☒ FI Finland | ☒ NI Nicaragua | ☒ VC Saint Vincent and the Grenadines |
| ☒ GB United Kingdom | ☒ NO Norway | ☒ VN Viet Nam |
| ☒ GD Grenada | ☒ NZ New Zealand | ☒ YU Serbia and Montenegro |
| ☒ GE Georgia | | ☒ ZA South Africa |
| ☒ GH Ghana | | ☒ ZM Zambia |
| ☒ GM Gambia | | ☒ ZW Zimbabwe |

Check-boxes below reserved for designating States which have become party to the PCT after issuance of this sheet:

- ☒ EG Egypt ☐ ☐

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (*Confirmation (including fees) must reach the receiving Office within the 15-month time limit.*)

Box No. VI PRIORITY CLAIM				
The priority of the following earlier application(s) is hereby claimed:				
Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country or Member of WTO	regional application: regional Office	international application: receiving Office
item (1) 25 July 2002 (25.07.02)	02 016 602.1	EP		
item (2)				
item (3)				
item (4)				
item (5)				
☐ Further priority claims are indicated in the Supplemental Box.				
The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office) identified above as: ☒ all items ☐ item (1) ☐ item (2) ☐ item (3) ☐ item (4) ☐ item (5) ☐ other, see Supplemental Box				
* Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii)):				
Box No. VII INTERNATIONAL SEARCHING AUTHORITY				
Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used): ISA / EP				
Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority): Date (day/month/year) Number Country (or regional Office) 26.09.2002 02 016 602.1 EP				
Box No. VIII DECLARATIONS				
The following declarations are contained in Boxes Nos. VIII (i) to (v) (mark the applicable check-boxes below and indicate in the right column the number of each type of declaration):				Number of declarations
☐ Box No. VIII (i)	Declaration as to the identity of the inventor			:
☐ Box No. VIII (ii)	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent			:
☐ Box No. VIII (iii)	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application			:
☐ Box No. VIII (iv)	Declaration of inventorship (only for the purposes of the designation of the United States of America)			:
☐ Box No. VIII (v)	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty			:

5X

Box No. IX CHECK LIST; LANGUAGE OF FILING																																																								
This international application contains: (a) In paper form, the following number of sheets: <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 80%;">request (including declaration sheets) :</td> <td style="width: 20%; text-align: right;">5</td> </tr> <tr> <td>description (excluding sequence listings and/or tables related thereto) :</td> <td style="text-align: right;">23</td> </tr> <tr> <td>claims :</td> <td style="text-align: right;">2</td> </tr> <tr> <td>abstract :</td> <td style="text-align: right;">1</td> </tr> <tr> <td>drawings :</td> <td style="text-align: right;">7</td> </tr> <tr> <td>Sub-total number of sheets :</td> <td style="text-align: right;">38</td> </tr> <tr> <td>sequence listings :</td> <td></td> </tr> <tr> <td>tables related thereto :</td> <td></td> </tr> <tr> <td colspan="2"><i>(for both, actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (c) below)</i></td> </tr> <tr> <td>Total number of sheets :</td> <td style="text-align: right;">38</td> </tr> </table> (b) ☐ only in computer readable form (Section 801(a)(i)) (i) ☐ sequence listings (ii) ☐ tables related thereto (c) ☐ also in computer readable form (Section 801(a)(ii)) (i) ☐ sequence listings (ii) ☐ tables related thereto Type and number of carriers (diskette, CD-ROM, CD-R or other) on which are contained the ☐ sequence listings: ☐ tables related thereto: <i>(additional copies to be indicated under items 9(i) and/or 10(i), in right column)</i>	request (including declaration sheets) :	5	description (excluding sequence listings and/or tables related thereto) :	23	claims :	2	abstract :	1	drawings :	7	Sub-total number of sheets :	38	sequence listings :		tables related thereto :		<i>(for both, actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (c) below)</i>		Total number of sheets :	38	This international application is accompanied by the following item(s) (mark the applicable check-boxes below and indicate in right column the number of each item): <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 80%;">1. ☒ fee calculation sheet</td> <td style="width: 20%; text-align: right;">1</td> </tr> <tr> <td>2. ☒ original separate power of attorney</td> <td style="text-align: right;">1</td> </tr> <tr> <td>3. ☐ original general power of attorney</td> <td style="text-align: right;"></td> </tr> <tr> <td>4. ☐ copy of general power of attorney; reference number, if any:</td> <td style="text-align: right;"></td> </tr> <tr> <td>5. ☐ statement explaining lack of signature</td> <td style="text-align: right;"></td> </tr> <tr> <td>6. ☐ priority document(s) identified in Box No. VI as item(s):</td> <td style="text-align: right;"></td> </tr> <tr> <td>7. ☐ translation of international application into (language):</td> <td style="text-align: right;"></td> </tr> <tr> <td>8. ☐ separate indications concerning deposited microorganism or other biological material</td> <td style="text-align: right;"></td> </tr> <tr> <td>9. ☐ sequence listings in computer readable form (Indicate type and number of carriers)</td> <td style="text-align: right;"></td> </tr> <tr> <td style="margin-left: 20px;">(i) ☐ copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application) :</td> <td style="text-align: right;"></td> </tr> <tr> <td style="margin-left: 20px;">(ii) ☐ (only where check-box (b)(i) or (c)(i) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Rule 13ter :</td> <td style="text-align: right;"></td> </tr> <tr> <td style="margin-left: 20px;">(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listings mentioned in left column :</td> <td style="text-align: right;"></td> </tr> <tr> <td>10. ☐ tables in computer readable form related to sequence listings (Indicate type and number of carriers)</td> <td style="text-align: right;"></td> </tr> <tr> <td style="margin-left: 20px;">(i) ☐ copy submitted for the purposes of international search under Section 802(b-quarter) only (and not as part of the international application) :</td> <td style="text-align: right;"></td> </tr> <tr> <td style="margin-left: 20px;">(ii) ☐ (only where check-box (b)(i) or (c)(i) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Section 802(b-quarter) :</td> <td style="text-align: right;"></td> </tr> <tr> <td style="margin-left: 20px;">(iii) ☐ together with relevant statement as to the identity of the copy or copies with the tables mentioned in left column :</td> <td style="text-align: right;"></td> </tr> <tr> <td>11. ☐ other (specify):</td> <td style="text-align: right;"></td> </tr> </table>	1. ☒ fee calculation sheet	1	2. ☒ original separate power of attorney	1	3. ☐ original general power of attorney		4. ☐ copy of general power of attorney; reference number, if any:		5. ☐ statement explaining lack of signature		6. ☐ priority document(s) identified in Box No. VI as item(s):		7. ☐ translation of international application into (language):		8. ☐ separate indications concerning deposited microorganism or other biological material		9. ☐ sequence listings in computer readable form (Indicate type and number of carriers)		(i) ☐ copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application) :		(ii) ☐ (only where check-box (b)(i) or (c)(i) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Rule 13ter :		(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listings mentioned in left column :		10. ☐ tables in computer readable form related to sequence listings (Indicate type and number of carriers)		(i) ☐ copy submitted for the purposes of international search under Section 802(b-quarter) only (and not as part of the international application) :		(ii) ☐ (only where check-box (b)(i) or (c)(i) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Section 802(b-quarter) :		(iii) ☐ together with relevant statement as to the identity of the copy or copies with the tables mentioned in left column :		11. ☐ other (specify):		Number of items
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Figure of the drawings which should accompany the abstract: 3	Language of filing of the international application: GB																																																							
Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE <i>Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).</i>																																																								
<table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; vertical-align: top;"> BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG pps. Dr. Reinfried ROTHERMEL </td> <td style="width: 50%; vertical-align: top;"> I.A. Dr. Gauthier OBRECHT </td> </tr> </table>			BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG pps. Dr. Reinfried ROTHERMEL	I.A. Dr. Gauthier OBRECHT																																																				
BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG pps. Dr. Reinfried ROTHERMEL	I.A. Dr. Gauthier OBRECHT																																																							

For receiving Office use only	
1. Date of actual receipt of the purported international application:	2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 1(2):	
5. International Searching Authority (if two or more are competent): ISA /	
6. ☐ Transmittal of search copy delayed until search fee is paid	
For International Bureau use only	
Date of receipt of the record copy by the International Bureau:	

Eingang CD Patents		
06. Okt. 2003		
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PATENT COOPERATION TREATY

EINGEGANGEN

06. Okt. 2003

Erled.

From the INTERNATIONAL BUREAU

To:

BOEHRINGER INGELHEIM PHARMA GMBH
& CO. KG
65216 Ingelheim am Rhein
Germany

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

Date of mailing (day/month/year) 25 September 2003 (25.09.03)	
Applicant's or agent's file reference Case 1/1370	IMPORTANT NOTIFICATION
International application No. PCT/EP03/07929	International filing date (day/month/year) 21 July 2003 (21.07.03)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 25 July 2002 (25.07.02)
Applicant BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
3. An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
4. The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
25 July 2002 (25.07.02)	02016602.1	EP	16 Sept 2003 (16.09.03)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 338.89.75	Authorized officer A. ZOLTANSKI (Fax : 338 89 75) Telephone No. (41-22) 338 8808
--	--

PATENT COOPERATION TREATY

56

EINGEGANGEN
13. Feb. 2004
Erledigt

PCT

From the INTERNATIONAL BUREAU

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

To:

BOEHRINGER INGELHEIM
& CO. KG
55216 Ingelheim am Rhein
Germany

Eingang CD Patents
PHARMA GMBH

02 Feb. 2004

SB	gesehen	erledigt
40	62	

Date of mailing (day/month/year) 27 January 2004 (27.01.2004)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference Case 1/1370	
International application No. PCT/EP2003/007929	International filing date (day/month/year) 21 July 2003 (21.07.2003)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address SEIDLER, Randolph 314 Avalon Lake Dr. Danbury, CT 06810 United States of America	State of Nationality DE	State of Residence US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address SEIDLER, Randolph 4 Lester Road Sandy Hook, CT 06482 United States of America	State of Nationality DE	State of Residence US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office ☐ the designated Offices concerned
☒ the International Searching Authority ☐ the elected Offices concerned
☐ the International Preliminary Examining Authority ☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 338.89.75	Authorized officer Mathieu BLANC (Fax 338 89 75) Telephone No. (41-22) 338 8988
--	---

From the INTERNATIONAL BUREAU

PCTNOTICE INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL
APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:

BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG
55216 Ingelheim am Rhein
ALLEMAGNE

Eingang CD Patents

18. Feb. 2004

SB	gesehen	erledigt
70	20	

EINGEGANGEN
18. Feb. 2004
Erled.

IMPORTANT NOTICE

Date of mailing (day/month/year)
05 February 2004 (05.02.2004)Applicant's or agent's file reference
Case 1/1370International application No.
PCT/EP2003/007929International filing date (day/month/year)
21 July 2003 (21.07.2003)Priority date (day/month/year)
25 July 2002 (25.07.2002)

Applicant

BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this notice:

AU, AZ, BY, CH, CN, CO, DE, DZ, EP, HU, JP, KG, KP, KR, MD, MK, MZ, RU, TM, US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

AE, AG, AL, AM, AP, AT, BA, BB, BG, BR, BZ, CA, CR, CU, CZ, DK, DM, EA, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, ID, IL, IN, IS, KE, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MG, MN, MW, MX, NI, NO, NZ, OA, OM, PG, PH, PL, PT, RO, SC, SD, SE, SG, SK, SL, SY, TJ, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this notice is a copy of the international application as published by the International Bureau on 05 February 2004 (05.02.2004) under No. WO 2004/011006

4. **TIME LIMITS** for filing a demand for international preliminary examination and for entry into the national phase

The applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be 30 MONTHS from the priority date, not only in respect of any elected Office if a demand for international preliminary examination is filed before the expiration of 19 months from the priority date, but also in respect of any designated Office, in the absence of filing of such demand, where Article 22(1) as modified with effect from 1 April 2002 applies in respect of that designated Office. For further details, see *PCT Gazette* No. 44/2001 of 1 November 2001, pages 19926, 19932 and 19934, as well as the *PCT Newsletter*, October and November 2001 and February 2002 issues.

In practice, time limits other than the 30-month time limit will continue to apply, for various periods of time, in respect of certain designated or elected Offices. For regular updates on the applicable time limits (20, 21, 30 or 31 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at <http://www.wipo.int/pct/en/index.html>.

For filing a demand for international preliminary examination, see the *PCT Applicant's Guide*, Volume I/A, Chapter IX. Only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II).

It is the applicant's sole responsibility to monitor all these time limits.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Gijsbertus Beijer - Carlos Roy

Facsimile No.(41-22) 740.14.35

Telephone No.(41-22) 338.91.11

Eingang CD Patents

02. März 2004

PATENT COOPERATION TREATY

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SE	gesehen	erledigt
20		PCT

From the INTERNATIONAL BUREAU

To:

BOEHRINGER INGELHEIM PHARMA GMBH
& CO. KG
55216 Ingelheim am Rhein
Germany

EINGEGANGEN

04. März 2004

Erledigt

INFORMATION CONCERNING ELECTED
OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

Date of mailing (day/month/year) 24 February 2004 (24.02.2004)		IMPORTANT INFORMATION	
Applicant's or agent's file reference Case 1/1370			
International application No. PCT/EP2003/007929	International filing date (day/month/year) 21 July 2003 (21.07.2003)	Priority date (day/month/year) 25 July 2002 (25.07.2002)	
Applicant BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG et al			

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

EP : AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR

National : BG, CA, CN, DE, GB, IL, JP, KP, KR, MN, NO, PL, RO, RU, SK, US

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

AP : GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW

EA : AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

OA : BF, BJ, CF, CG, CI, CM, GA, GN, GO, GW, ML, MR, NE, SN, TD, TG

National : AE, AG, AL, AM, AT, AU, AZ, BA, BB, BR, BY, BZ, CH, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, ES, FI, GD, GE, GH, GM, HR, HU, ID, IN, IS, KE, KG, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MW, MX, MZ, NI, NZ, OM, PG, PH, PT, SC, SD, SE, SG, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW

3. The applicant is reminded that he must enter the "national phase" before the expiration of 30 months from the priority date before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing, if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 38(3)(b) and Rule 74.1).

Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

The entry into the European regional phase is postponed until 31 months from the priority date for all States designated for the purposes of obtaining a European patent.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer: Aurora CENDANA (Fax : 338 89 75)
Facsimile No. (41-22) 338.89.75	Telephone No. (41-22) 338 8905

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ _____

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty.

For International Preliminary Examining Authority use only	
Identification of IPEA	Date of receipt of DEMAND
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION Applicant's or agent's file reference Case 1/1370	
International application No. PCT/EP 03/07929	International filing date (day/month/year) 21 July 2003 (21/07/03)
(Earliest) Priority date (day/month/year) 25 July 2002 (25/07/02)	
Title of invention USE OF A SPECIFIC CYCLIC AMINE DERIVATIVE OR THE PHARMACEUTICALLY ACCEPTABLE SALTS THEREOF FOR THE TREATMENT OR PREVENTION OF HEART FAILURE	
Box No. II APPLICANT(S)	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) Boehringer Ingelheim Pharma GmbH & Co. KG 55216 Ingelheim/Rhein DE	Telephone No. 07351-54-4390 Facsimile No. 07351-54-4377 Teleprinter No. Applicant's registration No. with the Office
State (that is, country) of nationality: DE	State (that is, country) of residence: DE
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) GUTH, Brian Kirchensteige 12 88447 Warthausen DE	
State (that is, country) of nationality: DE	State (that is, country) of residence: US
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) DAEMMGEN, Juergen Hattenburg Mittelbacherstrasse 1/2 88416 Ochsenhausen DE	
State (that is, country) of nationality: DE	State (that is, country) of residence: DE
☒ Further applicants are indicated on a continuation sheet.	

Continuation of Box No. II APPLICANT(S) <i>If none of the following sub-boxes is used, this sheet should not be included in the demand.</i>	
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)</i> SEIDLER, Randolph 4 Lester Road Sandy Hook, CT 06482 USA	
State <i>(that is, country)</i> of nationality: DE	State <i>(that is, country)</i> of residence: DE
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)</i> 	
State <i>(that is, country)</i> of nationality:	State <i>(that is, country)</i> of residence:
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)</i> 	
State <i>(that is, country)</i> of nationality:	State <i>(that is, country)</i> of residence:
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)</i> 	
State <i>(that is, country)</i> of nationality:	State <i>(that is, country)</i> of residence:
☐ Further applicants are indicated on another continuation sheet.	

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCEThe following person is ☐ agent ☐ common representativeand ☐ has been appointed earlier and represents the applicant(s) also for international preliminary examination.☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Telephone No.

Facsimile No.

Teleprinter No.

Agent's registration No. with the Office

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.**Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION****Statement concerning amendments:***

1. The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filedthe description ☒ as originally filed
☐ as amended under Article 34the claims ☐ as originally filed
☒ as amended under Article 19 (together with any accompanying statement)
☐ as amended under Article 34the drawings ☒ as originally filed
☐ as amended under Article 342. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of the applicable time limit under Rule 69.1(d).4. ☒ The applicant expressly wishes the international preliminary examination to start earlier than at the expiration of the applicable time limit under Rule 54bis.1(a).

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English

☒ which is the language in which the international application was filed.☐ which is the language of a translation furnished for the purposes of international search.☐ which is the language of publication of the international application.☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.**Box No. V ELECTION OF STATES**

The filing of this demand constitutes the election of all Contracting States which are designated and are bound by Chapter II of the PCT.

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:			For International Preliminary Examining Authority use only	
			received	not received
1.	translation of international application	: sheets	☐	☐
2.	amendments under Article 34	: sheets	☐	☐
3.	copy (or, where required, translation) of amendments under Article 19	: 3 sheets	☐	☐
4.	copy (or, where required, translation) of statement under Article 19	: 1 sheets	☐	☐
5.	letter	: 2 sheets	☐	☐
6.	other (specify)	: sheets	☐	☐

- The demand is also accompanied by the item(s) marked below:
- | | |
|--|--|
| 1. ☒ fee calculation sheet | 5. ☐ statement explaining lack of signature |
| 2. ☐ original separate power of attorney | 6. ☐ sequence listing in computer readable form |
| 3. ☐ original general power of attorney | 7. ☐ tables in computer readable form related to a sequence listing |
| 4. ☐ copy of general power of attorney; reference number, if any: | 8. ☐ other (specify): |

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE
Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

Boehringer Ingelheim Pharma GmbH & Co. KG

ppa. 	IA 
Dr. Reinfried ROTHERMEL	Dr. Gauthier OBRECHT

For International Preliminary Examining Authority use only

- | | |
|--|--|
| 1. Date of actual receipt of DEMAND: | |
| 2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b): | |
| 3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.
☐ The applicant has been informed accordingly. | 6. ☐ The date of receipt of the demand is AFTER the expiration of the time limit under Rule 54bis.1(a) and item 7 or 8, below, does not apply. |
| 4. ☐ The date of receipt of the demand is WITHIN the time limit of 19 months from the priority date as extended by virtue of Rule 80.5. | 7. ☐ The date of receipt of the demand is WITHIN the time limit under Rule 54bis.1(a) as extended by virtue of Rule 80.5. |
| 5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82. | 8. ☐ Although the date of receipt of the demand is after the expiration of the time limit under Rule 54bis.1(a), the delay in arrival is EXCUSED pursuant to Rule 82. |

For International Bureau use only

Demand received from IPEA on:

PATENT CO PERATION TREATY

→ Kug : 2. Info

10. Feb. 2004
Erled.

PCT

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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:		BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG D-55216 Ingelheim am Rhein ALLEMAGNE		NOTIFICATION OF RECEIPT OF DEMAND BY COMPETENT INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY (PCT Rules 59.3(e) and 61.1(b), first sentence and Administrative Instructions, Section 601(a))	
		Eingang PCT Patents 06. Feb. 2004			
		SB gesehen erledigt 10 60			
				Date of mailing (day/month/year) 05-02-2004	
Applicant's or agent's file reference case 1/1370				IMPORTANT NOTIFICATION	
International application No. PCT/EP03/07929		International filing date (day/month/year) 21/07/2003		Priority date (day/month/year) 25/07/2002	
Applicant BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG et al.					

1. The applicant is hereby notified that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application:

20/01/2004

2. This date of receipt is:

☒ the actual date of receipt of the demand by this Authority (Rule 61.1(b)).

☐ the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(e)).

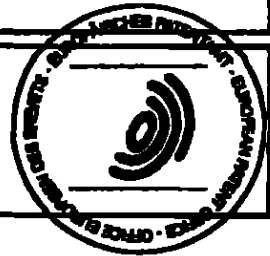
☐ the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IPEA/404), received the required corrections.

3. ☐ **ATTENTION:** That date of receipt is after the expiration of 19 months from the priority date. Consequently, in respect of some Offices, the demand does not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)) and the acts for entry into the national phase must therefore be performed within 20 months from the priority date (or later in some Offices). However, in respect of some other Offices, the time limit of 30 months (or later) may nevertheless apply. See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

☐ (If applicable) This notification confirms the information given by telephone, facsimile transmission or in person on:

4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

Name and mailing address of the IPEA/  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523636 eprnu d Fax: (+49-89) 2399-4465	Authorized officer FERRO VASCONCELOS M Tel. (+49-89) 2399-7905
--	---



PATENT COOPERATION TREATY

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64

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

BOEHRINGER INGELHEIM PHARMA GMBH
& CO. KG
D-55216 Ingelheim am Rhein
ALLEMAGNE

Eingang CD Patents

11 Mai 2004

PCT EINGEGANGEN
13 Mai 2004
WRITTEN OPINION
(PCT Rule 66)

SB	gesehen	erledigt	date of mailing
AD	6.5	60	(day/month/year)

10.05.2004

Applicant's or agent's file reference
case 1/1370

REPLY DUE

within 4 month(s)
from the above date of mailing

International application No.
PCT/EP 03/07929

International filing date (day/month/year)
21.07.2003

Priority date (day/month/year)
25.07.2002

International Patent Classification (IPC) or both national classification and IPC
A61K31/55, A61K31/55

Applicant

BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG et al.

1. This written opinion is the first drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(II) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

CD Patents
Frist: 10.09.04
Termin not: 10.07.04
TS.

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis. For an informal communication with the examiner, see Rule 66.8.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 25.11.2004

Name and mailing address of the international preliminary examining authority:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523668 epmu d
Fax: +49 89 2399 - 4485

Authorized Officer

Herrera, S

Formalities officer (incl. extension of time limits)
Ladumer, Y
Telephone No. +49 89 2399-7913



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WRITTEN OPINION

International application No. PCT/EP 03/07929

I. Basis of the opinion

1. With regard to the elements of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"*):

Description, Pages

1-23 as originally filed

Claims, Numbers

1-17 received on 24.11.2003 with letter of 24.11.2003

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

WRITTEN OPINIONInternational application No. **PCT/EP 03/07929**☐ the entire international application,☒ claims Nos. 17

because:

☒ the said international application, or the said claims Nos. 17 relate to the following subject matter which does not require an international preliminary examination (specify):**see separate sheet**☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.☐ no international search report has been established for the said claims Nos.

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the Standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.☐ the computer readable form has not been furnished or does not comply with the Standard.**V. Reasoned statement under Rule 68.2(a)(ii) with regard to novelty, Inventive step or Industrial applicability; citations and explanations supporting such statement****1. Statement**

Novelty (N)	Claims	
Inventive step (IS)	Claims	1-17
Industrial applicability (IA)	Claims	

2. Citations and explanations**see separate sheet**

Section III

Claim 17 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Section IV

1. The following documents (D) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:
D1: EP-A-0 471 388 (THOMAE GMBH DR K) 19 February 1992 (1992-02-19)
D2: WO 01 78699 A (BOEHRINGER INGELHEIM PHARMA ;GUTH BRIAN (DE);
DAEMMGEN JUERGEN (DE) 25 October 2001 (2001-10-25)
D3: EP-A-0 224 794 (THOMAE GMBH DR K) 10 June 1987 (1987-06-10)
2. The subject-matter of the present claims is novel over the prior art in that it was not known before to use cilobradine in the treatment of heart failure (Art 33(2) PCT).
4. It was however well known that cilobradine lowers the heart rate (e.g. D3, cf. parts indicated in the search report). It was further well known that the structurally close compound zatebradine (known for the same bradycardic effect, cf. D2) can be used in the treatment of heart failure because of its lowering effect on the heart rate (cf. parts indicated in the search report).
For the skilled person it is obvious to try also cilobradine for its effect on heart failure because of the structural similarity with zatebradine combined with the knowledge that both compounds have a lowering effect on the heart rate.
Additionally the skilled person would expect a better effect on cilobradine than with zatebradine since cilobradine have a better effect on the heart rate.
The subject-matter of the present claims therefore fails to fulfill the requirements of Article 33 (3) PCT because of lack of inventive step.

PATENT COOPERATION TREATY

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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

EINGEGANGEN

PCT

To:

BOEHRINGER INGELHEIM PHARMA GMBH
& CO. KG
D-55216 Ingelheim am Rhein
ALLEMAGNE

Eingang CD Patents

25. Okt. 2004

25. Okt. 2004

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

(PCT Rule 71.1)

SB	gesehen	erledigt
60	60	

Date of mailing
(day/month/year)

22.10.2004

Applicant's or agent's file reference
case 1/1370

IMPORTANT NOTIFICATION

International application No.
PCT/EP 03/07928

International filing date (day/month/year)
21.07.2003

Priority date (day/month/year)
25.07.2002

Applicant

BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the International
preliminary examining authority:



European Patent Office
D-80296 Munich
Tel. +49 89 2399 - 0 Tx: 523856 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Ladumer, Y

Tel. +49 89 2399-7913



PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)

Applicant's or agent's file reference case 1/1370	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEAA16)	
International application No. PCT/EP 03/07929	International filing date (day/month/year) 21.07.2003	Priority date (day/month/year) 25.07.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/55		
Applicant BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG et al.		
1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of 4 sheets, including this cover sheet. ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 807 of the Administrative Instructions under the PCT). These annexes consist of a total of sheets. 3. This report contains indications relating to the following items: - I ☒ Basis of the opinion - II ☐ Priority - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability - IV ☐ Lack of unity of invention - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement - VI ☐ Certain documents cited - VII ☐ Certain defects in the international application - VIII ☐ Certain observations on the international application		
Date of submission of the demand 20.01.2004	Date of completion of this report 22.10.2004	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 23699 - 0 Tx: 523658 spmu d Fax: +49 89 23699 - 4465	Authorized Officer Herrera, S Telephone No. +49 89 23699-6464 	

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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/EP 03/07929**

I. Basis of the report

1. With regard to the elements of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1-23 as originally filed

Claims, Numbers

1-17 received on 24.11.2003 with letter of 24.11.2003

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/EP 03/07929**

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 17
because:
 - ☒ the said international application, or the said claims Nos. 17 relate to the following subject matter which does not require an international preliminary examination (specify):
see separate sheet
 - ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
 - ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
 - ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the Standard.
- ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-17
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-17
Industrial applicability (IA)	Yes: Claims	1-16
	No: Claims	

2. Citations and explanations

see separate sheet

Section III

Claim 17 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Section V

1. The following documents (D) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:
D1: EP-A-0 471 388 (THOMAE GMBH DR K) 19 February 1992 (1992-02-19)
D2: WO 01 78699 A (BOEHRINGER INGELHEIM PHARMA ;GUTH BRIAN (DE);
DAEMMGEN JUERGEN (DE) 25 October 2001 (2001-10-25)
D3: EP-A-0 224 794 (THOMAE GMBH DR K) 10 June 1987 (1987-06-10)
2. The subject-matter of the present claims is novel over the prior art in that it was not known before to use cilobradine in the treatment of heart failure (Art 33(2) PCT).
4. It was however well known that cilobradine lowers the heart rate (e.g. D3, cf. parts indicated in the search report). It was further well known that the structurally close compound zatebradine (known for the same bradycardic effect, cf. D2) can be used in the treatment of heart failure because of its lowering effect on the heart rate (cf. parts indicated in the search report).
For the skilled person it is obvious to try also cilobradine for its effect on heart failure because of the structural similarity with zatebradine combined with the knowledge that both compounds have a lowering effect on the heart rate.
Additionally the skilled person would expect a better effect on cilobradine than with zatebradine since cilobradine have a better effect on the heart rate.
The subject-matter of the present claims therefore fails to fulfill the requirements of Article 33 (3) PCT because of lack of inventive step.

CLAIMS

1. Use of cilobradine or a pharmaceutically acceptable salt thereof for the preparation of a pharmaceutical composition for the treatment or prevention of heart failure.
2. Use in accordance with claim 1, wherein the pharmaceutical composition is for the prevention of heart failure.
3. Use in accordance with claim 1, wherein the pharmaceutical composition is for the treatment or prevention of diastolic heart failure.
4. Use in accordance with claim 3, wherein the pharmaceutical composition is for the prevention of diastolic heart failure.
5. Use in accordance with claim 1, wherein the pharmaceutical composition is for the treatment or prevention of systolic heart failure.
6. Use in accordance with claim 5, wherein the pharmaceutical composition is for the prevention of systolic heart failure.
7. Use in accordance with any one of claims 1 to 6, wherein the galenical formulation of the pharmaceutical composition is a tablet, a drinking solution, a capsule, a suppository or an injectable formulation.
8. Use in accordance with any one of claims 1 to 7, wherein the galenical formulation of the pharmaceutical composition is a tablet.

9. Use in accordance with any one of claims 1 to 7, wherein the galenical formulation of the pharmaceutical composition is a drinking solution.

10. Use in accordance with any one of claims 1 to 9, wherein the pharmaceutical composition is to be administered following a single or multiple stage daily application scheme.

11. Use in accordance with claim 10, wherein cilobradine or its pharmaceutically acceptable salt is to be administered between 0.01 and 20 mg/kg body weight.

12. Use in accordance with claim 10, wherein cilobradine or its pharmaceutically acceptable salt is to be administered between 0.05 and 5 mg/kg body weight.

13. Use in accordance with claim 10, wherein cilobradine or its pharmaceutically acceptable salt is to be administered between 0.1 and 2.5 mg/kg body weight.

14. Use in accordance with claim 10, wherein cilobradine or its pharmaceutically acceptable salt is to be administered between 0.1 and 1 mg/kg body weight.

15. Use in accordance with claim 10, wherein cilobradine or its pharmaceutically acceptable salt is to be administered between 0.1 and 0.75 mg/kg body weight.

16. Use in accordance with any one of claims 1 to 15, wherein the treatment or prevention of heart failure is performed in combination with other therapeutic agents for the treatment or prevention of heart failure, such as diuretics, cardiac glycosides, ACE inhibitors, ARBs, vasodilators, beta blockers or inotropes.

17. A method for the treatment or prevention of heart failure, which comprises the administration to a patient in need thereof of a pharmaceutical composition comprising cilobradine or a pharmaceutically acceptable salt thereof, together with a pharmaceutically suitable carrier.

TRATADO DE COOPERACIÓN DE PATENTES
PCT
INFORME DE EXAMEN PRELIMINAR INTERNACIONAL
(Artículo 36 y Regla 70 del PCT)

Referencia del expediente del agente o solicitante CASE 1/1370	PARA ACTUACIONES ADICIONALES	Ver notificación de Transmisión del Reporte de Examen Preliminar (Formato PCT/IPEA416)
Solicitud Internacional No. PCT/EP03/07829	Fecha de presentación Internacional (día/mes/año) 21.07.2003	Fecha de prioridad (día/mes/año) 25.07.2002
Clasificación Internacional de Patentes (IPC) o clasificación nacional a IPC A61K 31/55		
Solicitante BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG et al		

1. Este informe de examen preliminar internacional ha sido preparado por esta Administración encargada del Examen Preliminar Internacional y se envía al solicitante en concordancia con el artículo 36.

2. Este INFORME consta de una total de 4 hojas, incluyendo la portada

☐ Este Informe también se acompaña de ANEXOS, esto es documentos de la descripción, reivindicaciones y/o dibujos que han sido corregidos y que son la base de este Informe y/o documentos que contienen rectificaciones realizadas ante esta Administración (Ver Regla 70.16 y Sección 607 de las Instrucciones Administrativas según el PCT)

Estos anexos constan de un total de _____ hojas.

3. Este informe contiene indicaciones relativas a los siguientes aspectos:

I ☒ Fundamentos del Informe

II ☐ Prioridad

III ☒ No se establece concepto relativo a la novedad, nivel inventivo y aplicación industrial

IV ☐ Carencia de unidad de la invención

V ☒ Declaración razonada según el artículo 35(2), en relación con la novedad, nivel inventivo o aplicación industrial; citaciones y explicaciones que soportan dicha declaración

VI ☐ Ciertos documentos citados

VII ☐ Ciertos defectos de la solicitud internacional

VIII ☐ Ciertas observaciones respecto a la solicitud internacional

Fecha de presentación de la demanda 20.01.2004	Fecha de terminación de este reporte 22.10.2004
Nombre y dirección de correo de la autoridad encargada del examen preliminar  Oficina Europea de Patentes D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 apmu d Fax: +49 89 2399 - 4465	Funcionario Autorizado Herrera, S Teléfono No. +49 89 2399-8464

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I. Base del Informe

1. Respecto a los elementos de la solicitud internacional: *(Las hojas de reemplazo que han sido entregadas a la Oficina receptora en respuesta a la invitación bajo el Artículo 14 se refieren en este informe como "originalmente presentadas" y no se anexan a este informe ya que ellas no contienen modificaciones (Regla 70.16 y 70.17)).*

La descripción, páginas

1 – 23 como se presentaron originalmente

Las reivindicaciones, números

1 – 17 recibidas el 24.11.2003 junto con carta 24.11.2003

2. Respecto al lenguaje, todos los elementos marcados anteriormente estuvieron disponibles o fueron enviados a la Administración en el lenguaje en que se presentó la solicitud internacional, a menos que se indique otra cosa en este punto.

Estos elementos estuvieron disponibles o fueron enviados a esta Administración en el siguiente lenguaje _____ el cual es:

- ☐ el lenguaje de la traducción enviada para propósitos de la búsqueda internacional (bajo Regla 23.1 (b)).
☐ el lenguaje de la publicación de la solicitud internacional (bajo Regla 48.3(b)).
☐ el lenguaje de la traducción entregada con propósitos del examen preliminar internacional (bajo Regla 55.2 y/o 55.3).

3. Respecto a cualquier secuencia de nucleótido y/o amino ácidos divulgada en la solicitud internacional, el examen preliminar internacional se llevó a cabo con base en el listado de secuencias:

- ☐ contenido en la solicitud internacional en forma escrita
☐ presentado junto con la solicitud internacional en forma legible por computador
☐ entregado posteriormente a esta Administración en forma legible por computador
☐ La declaración de que el listado de secuencias posteriormente entregado no va más allá de lo divulgado en la solicitud internacional originalmente presentada, ha sido entregada.
☐ La declaración de que la información grabada en la forma legible por computador es idéntica al listado de secuencias escrito que se ha entregado.

4. ☐ Las modificaciones han dado como resultado la cancelación de:

- ☐ la descripción, páginas _____.
☐ las reivindicaciones, Nos. _____.
☐ los dibujos, página _____.

5. ☐ Este reporte ha sido establecido como si (parte de) las modificaciones no se hubieran realizado, ya que éstas han sido consideradas como una ampliación de lo inicialmente divulgado como se indica en la Casilla Suplementaria (Regla 70.2(c)).

(Cualquier hoja de reemplazo que contenga dichas modificaciones deberá ser referida bajo el punto 1 y anexada a este informe.)

6. Observaciones adicionales, si es necesario:

Formato PCT/IPEA/409 (Recuadro I) (julio 1998)

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III. No establecimiento de opinión con respecto a la novedad, nivel inventivo y aplicabilidad Industrial.

1. La pregunta de si la invención reivindicada parece tener novedad, nivel inventivo (que no sea obvia), o que sea aplicable industrialmente no ha sido examinada con respecto a:

- ☐ la solicitud internacional completa
- ☒ las reivindicaciones Nos. 17

Porque

- ☒ la solicitud internacional, o las mencionadas reivindicaciones Nos. 17 se relacionan con los siguientes objetos, los cuales no requieren examen preliminar internacional (*especifique*):

Ver hoja separada

- ☐ la descripción, las reivindicaciones o los dibujos (*indique los elementos particulares abajo*) o las mencionadas reivindicaciones Nos. _____ son demasiado confusas que no se puede formar ninguna opinión significativa (*especifique*):
- ☐ la descripción, o las mencionadas reivindicaciones Nos. _____ no están adecuadamente soportadas por la descripción que no se puede formar ninguna opinión significativa.
- ☐ no se ha establecido un reporte de búsqueda para las mencionadas reivindicaciones Nos. _____

2. No se pudo realizar un examen preliminar internacional significativo debido a fallas en el listado de nucleótidos y/o aminoácidos para dar cumplimiento con los estándares del Anexo C de las Instrucciones Administrativas:

- ☐ El formato escrito no ha sido suministrado o no cumple con los estándares.
- ☐ El formato de lectura por computador no ha sido suministrado o no cumple con los estándares.

V. Declaración motivada según el Artículo 35(2) en cuanto a la novedad, el nivel inventivo y la aplicación Industrial; citas y explicaciones que apoyan esta declaración.

1. Declaración

Novedad (N)	SI	Reivindicaciones	<u>1 – 17</u>
	NO	Reivindicaciones	_____
Nivel inventivo (NI)	SI	Reivindicaciones	_____
	NO	Reivindicaciones	<u>1 – 17</u>
Aplicación Industrial (AI)	SI	Reivindicaciones	<u>1 – 16</u>
	NO	Reivindicaciones	_____

2. Citas y explicaciones (Regla 70.7)

Ver hoja separada

Sección III

La reivindicación 17 se relaciona con un objeto que es considerado por esta Autoridad como que se encuentra cubierto por lo provisto en la Regla 67.1 (iv) PCT. Consecuentemente, no se formulará una opinión con respecto a la aplicabilidad industrial del objeto de las reivindicaciones (Artículo 34 (4)(a)(i) PCT).

Sección V

1. Se hace referencia a los siguientes documentos (D) en la presente comunicación; la numeración será mencionada en el resto del procedimiento:
D1: EP-A-0 471 388 (THOMAE GMBH DR K) 19 de Febrero de 1992 (1992-02-19)
D2: WO 01 78699 A (BOEHRINGER INGELHEIM PHARMA; GUTH BRIAN (DE); DAEMMGEN JUERGEN (DE)) 25 de Octubre de 2001 (2001-10-25)
D3: EP-A-0 224 794 (THOMAE GMBH DR K) 10 de Junio de 1987 (1987-06-10)
2. El objeto de las presentes reivindicaciones son novedosas sobre el arte previo en el sentido de que el uso de la cilobradina en el tratamiento de la falla cardíaca no era conocido (Art 33(2) PCT)
3. Sin embargo, era bien conocido que la cilobradina reduce la frecuencia cardíaca (por ejemplo, D3, c, partes indicadas en el informe de búsqueda). Se conocía además que el compuesto estructuralmente cercano zatebradina (conocido para el mismo efecto bradicárdico, cf D2) puede ser usado en el tratamiento de la falla cardíaca debido a su efecto reductor de la frecuencia cardíaca (cf. Partes indicadas en el Informe de búsqueda)

Para una persona versada en la materia es obvio ensayar también la cilobradina para este efecto sobre la falla cardíaca debido a su similitud estructural con la zatebradina combinada con el conocimiento de que ambos compuestos tienen un efecto reductor de la frecuencia cardíaca. Adicionalmente dicha persona versada esperaría un efecto mejorado con la cilobradina que con la zatebradina debido a que la cilobradina tiene un mejor efecto sobre la frecuencia cardíaca.

El objeto de las presentes reivindicaciones entonces falla para cumplir los requerimientos del Artículo 33(3) PCT debido a la falta de nivel inventivo.

REIVINDICACIONES

1. Uso de cilobradina o una sal farmacéuticamente aceptable de la misma para la preparación de una preparación farmacéutica para el tratamiento o prevención de la falla cardíaca.
2. Uso de acuerdo con la reivindicación 1, en donde la preparación farmacéutica es para el tratamiento o prevención de la falla cardíaca.
3. Uso de acuerdo con la reivindicación 1, en donde la preparación farmacéutica es para el tratamiento o prevención de la falla cardíaca diastólica.
4. Uso de acuerdo con la reivindicación 3, en donde la preparación farmacéutica es para la prevención de la falla cardíaca diastólica.
5. Uso de acuerdo con la reivindicación 1, en donde la preparación farmacéutica es para el tratamiento o prevención de la falla cardíaca sistólica.
6. Uso de acuerdo con la reivindicación 5, en donde la preparación farmacéutica es para la prevención de la falla cardíaca sistólica.
7. Uso de acuerdo con cualquiera de las reivindicaciones 1 a 6, en donde la forma farmacéutica de la preparación farmacéutica es una tableta, una solución ingerible, una cápsula, un supositorio o una formulación inyectable.
8. Uso de acuerdo con cualquiera de las reivindicaciones 1 a 7, en donde la forma farmacéutica de la preparación farmacéutica es una tableta.
9. Uso de acuerdo con cualquiera de las reivindicaciones 1 a 7, en donde la forma farmacéutica de la preparación farmacéutica es una solución ingerible.
10. Uso de acuerdo con cualquiera de las reivindicaciones 1 a 9, en donde la preparación farmacéutica es administrada en un esquema de administración de aplicación diaria única o múltiple.

- 11. Uso de acuerdo con la reivindicación 10, en donde la cilobradina o su sal farmacéuticamente aceptable es administrada en una cantidad de 0.01 y 20 mg/kg de peso corporal.
- 12. Uso de acuerdo con la reivindicación 10, en donde la cilobradina o su sal farmacéuticamente aceptable es administrada en una cantidad de 0.05 y 5 mg/kg de peso corporal.
- 13. Uso de acuerdo con la reivindicación 10, en donde la cilobradina o su sal farmacéuticamente aceptable es administrada en una cantidad de 0.1 y 2.5 mg/kg de peso corporal.
- 14. Uso de acuerdo con la reivindicación 10, en donde la cilobradina o su sal farmacéuticamente aceptable es administrada en una cantidad de 0.1 y 1 mg/kg de peso corporal.
- 15. Uso de acuerdo con la reivindicación 10, en donde la cilobradina o su sal farmacéuticamente aceptable es administrada en una cantidad de 0.1 y 0.75 mg/kg de peso corporal.
- 16. Uso de acuerdo con cualquiera de las reivindicaciones 1 a 15, en donde el tratamiento o prevención de la falla cardíaca se realiza en combinación con otros agentes terapéuticos para el tratamiento o prevención de la falla cardíaca, tales como diuréticos, glicósidos cardíacos, Inhibidores de la ECA, ARBs, vasodilatadores, beta bloqueadores o inotrópicos.
- 17. Un método para el tratamiento o prevención de la falla cardíaca, el cual comprende administrarle a un paciente que lo necesite una composición farmacéutica que comprende cilobradina o una sal farmacéuticamente aceptable de la misma, junto con un vehículo farmacéuticamente aceptable.

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**USO DE UN DERIVADO DE AMINA CÍCLICA ESPECÍFICO O DE SUS
SALES FARMACÉUTICAMENTE ACEPTABLES PARA TRATAR O
PREVENIR LA INSUFICIENCIA CARDIACA**

5 CAMPO DE LA INVENCION

La presente Invención se refiere al nuevo uso de un derivado de amina cíclica, concretamente la cilobradina, o sus sales farmacéuticamente aceptables, para tratar o prevenir la insuficiencia cardiaca de cualquier etiología.

10 ANTECEDENTES DE LA INVENCION

La insuficiencia cardiaca es un importante problema de salud pública mundial y es el único trastorno cardiaco que está aumentando su incidencia. Sólo en los Estados Unidos, 5 millones de pacientes padecen insuficiencia cardiaca, haciéndose una nueva diagnosis en 0,5 millones de pacientes por año. A pesar de los avances en terapia en la última década, el número de hospitalizaciones anuales ha aumentado de 550.000 a 900.000 como diagnosis primaria, y de 1,7 a 2,6 millones como diagnosis primaria o secundaria (*J. Am. Pharm. Assoc.*, vol. 41(5), pp. 672-681, 2001). Si no se trata, la insuficiencia cardiaca puede conducir a la muerte. Por lo tanto, se justifican nuevos enfoques para tratar o prevenir la insuficiencia cardiaca.

Aunque la expresión insuficiencia cardiaca parece que es la expresión más aceptada para describir este trastorno cardiaco, se pueden encontrar otras expresiones equivalentes en la bibliografía científica, de patentes o médica, tal como por ejemplo, fallo cardiaco, gasto cardiaco insuficiente, insuficiencia del corazón, colapso cardiaco y síncope cardiaco.

Además, aunque la Insuficiencia cardiaca es invariablemente un trastorno cardiaco crónico, a menudo con una aparición insidiosa, la insuficiencia cardiaca puede estar presente de forma intensa o tener episodios de deterioro agudo, llamada insuficiencia cardiaca "descompensada". Para describir estos estados también relacionados con la Insuficiencia cardiaca, se encontrarán normalmente otras expresiones en la bibliografía científica, de patentes o médica, tales como por ejemplo, insuficiencia cardiaca crónica, insuficiencia cardiaca aguda, descompensación del corazón, descompensación cardiaca y descompensación cardial.

Finalmente, como se explicará en lo sucesivo, puesto que la insuficiencia cardiaca puede ser causada por una disfunción del corazón reflejada por diferentes cuadros clínicos y a veces sometida a otras

complicaciones, también se encontrarán otras expresiones relacionadas con la insuficiencia cardíaca en la bibliografía científica, de patentes o médica, tal como por ejemplo, fallo miocárdico, insuficiencia miocárdica, insuficiencia del músculo del corazón, insuficiencia del músculo cardíaco, debilidad del músculo del corazón, debilidad del músculo cardíaco, insuficiencia cardíaca sistólica o ventricular izquierda, insuficiencia cardíaca diastólica, insuficiencia cardíaca del lado izquierdo o derecho, insuficiencia cardíaca biventricular, e insuficiencia cardíaca congestiva.

Por lo tanto, se puede hacer una distinción entre el origen sistólico o diastólico de la disfunción. Normalmente, la insuficiencia cardíaca es consecuencia de un deterioro progresivo de la función contráctil del miocardio, llamada disfunción sistólica o ventricular izquierda. Sin embargo, la disfunción diastólica se está empezando a reconocer cada vez más como una causa también importante de la insuficiencia cardíaca. Ésta se produce cuando las cámaras del corazón no pueden expandirse suficientemente durante la diástole (período de relajación del corazón en el que las cámaras se llenan de sangre) y por lo tanto, el volumen de sangre en los ventrículos no es adecuado. Cuando la disfunción sistólica y/o diastólica es la base de la insuficiencia cardíaca, disminuye el gasto cardíaco. Cuando adicionalmente hay una "retención" del retorno de la sangre al sistema venoso, le puede seguir la congestión en los pulmones (edema pulmonar) y/o en el abdomen o periferias (edema periférico). Cuando se producen ambos, se usa a menudo la expresión insuficiencia cardíaca congestiva.

Por lo demás, la diferencia entre insuficiencia cardíaca de lado izquierdo y derecho se puede aplicar para reflejar el cuadro clínico (es decir, el edema pulmonar indicativo de insuficiencia cardíaca del lado izquierdo, mientras que el síntoma principal de la insuficiencia cardíaca del lado derecho es la retención de líquido en las periferias), o para indicar la causa subyacente. La insuficiencia cardíaca del lado derecho normalmente es una consecuencia de la insuficiencia cardíaca del lado izquierdo, aunque las enfermedades de pulmón (tales como enfermedad pulmonar obstructiva crónica), del ventrículo derecho (por ejemplo, infarto ventricular derecho) o de la vasculatura (hipertensión pulmonar primaria o secundaria, la última debida a estados tales como embolia pulmonar, por ejemplo), pueden dar como resultado que predomine la insuficiencia cardíaca del lado derecho.

De acuerdo con la Clasificación Internacional de Funcionamiento, Discapacidad y Salud, publicada finalmente por la Organización Mundial de la

Salud el 15 de Noviembre de 2001 (ISBN 91 4 1545429) y aceptada por 191 países durante la 54 Asamblea Mundial de la Salud (Resolución WHA 54.21), la insuficiencia cardíaca se produce cuando está afectada la función del corazón de bombeo de la sangre en cantidades adecuadas o requeridas y la presión en el cuerpo.

Puesto que el gasto cardíaco es normalmente 5 litros/minuto, aunque éste puede aumentar cinco veces con el ejercicio fuerte, en esencia, la insuficiencia cardíaca se produce cuando el corazón no puede satisfacer esta demanda.

Puesto que la propia insuficiencia cardíaca se manifiesta en una variedad de formas, en el momento de la solicitud de esta patente, el tratamiento o prevención de la insuficiencia cardíaca comprende una combinación de medicaciones típicas. Estas medicaciones se basan en los principios de promover la excreción de líquidos para reducir el edema y la sobrecarga de volumen (por ejemplo, diferentes tipos de diuréticos), fármacos vasodilatadores para reducir la precarga (es decir, presiones arteriales) y/o la postcarga (es decir, la presión contra la que tiene latir el corazón), y fármacos inotropos para aumentar la contractilidad.

Entre los fármacos vasodilatadores disponibles en este momento, se incluyen los inhibidores de la enzima convertidora de angiotensina (ECA), bloqueadores del receptor de angiotensina II (BRA) y venodilatadores tipo nitrato. Normalmente, los fármacos inotropos se administran sólo en situaciones agudas. Aunque a veces se prescriben glicósidos cardíacos tales como la digoxina por sus propiedades inotrópicas, su uso es más común en pacientes con insuficiencia cardíaca cuando coexiste con arritmias auriculares.

Recientemente, se ha mostrado que los beta bloqueadores, que antes se pensaba que estaban contraindicados en la insuficiencia cardíaca debido a su propiedad inotrópica negativa (disminución de la contractilidad), son eficaces en el tratamiento de la insuficiencia cardíaca. Metanálisis de ensayos controlados aleatorios han mostrado que, además de la terapia base establecida de inhibidores de la ECA y diuréticos con o sin digoxina, los beta-bloqueadores tales como carvedilol, metoprolol o bisoprolol, confieren una reducción de todas las causas de mortalidad y morbilidad cardiovascular (Brophy J. M. et al., *Ann. Intern. Med.* 2001, Vol. 134, pp. 550-560; Lechat P. et al., *Circ.* 1998, pp. 1184-1191; Heidenreich P. A. et al., *J. Am. Coll. Cardiol.*, 1997, Vol. 30, pp 27-34).

Cuando la insuficiencia cardíaca avanza, el tratamiento de la

insuficiencia cardiaca normalmente tampoco se limita a una sola terapia. De ahí que se describa el uso de terapia adyuvante para el carvedilol, por ejemplo, en el documento WO 96/24348, para disminuir la mortalidad de pacientes que padecen insuficiencia cardiaca congestiva. El documento WO 96/40258 describe una terapia de combinación que comprende un antagonista de la angiotensina II y espironolactona, un antagonista del receptor de aldosterona, para el tratamiento de la hipertensión, enfermedad cardiaca congestiva, cirrosis y ascitis. El documento WO 00/02543 describe una terapia de combinación que comprende un antagonista de la angiotensina II (valsartán) y un bloqueador del canal de calcio (amlodipina o verapamilo) para tratar varias enfermedades cardiacas, entre las que se citan las enfermedades cardiacas congestivas crónicas.

Sin embargo, como con todas las terapias, hay restricciones para su uso. Por ejemplo, los beta-bloqueadores pueden estar contraindicados en pacientes con enfermedades concomitantes tales como asma, enfermedad vascular periférica e insuficiencia cardiaca descompensada. Ciertas clases de fármacos pueden no ser tolerados debido a efectos secundarios no deseados, por ejemplo, tos con inhibidores de la ECA, fatiga, mareo o impotencia asociados con beta-bloqueadores, e hiponatremia con diuréticos. Además, puede ser necesario un periodo lento y cuidadoso de valoración cuando se empieza con el fármaco, como con los beta-bloqueadores, donde si no se lleva a cabo, los efectos negativos iniciales en la acción de bombeo del corazón (inotropía negativa) pueden dar como resultado la intolerancia del fármaco y el deterioro del estado de la insuficiencia cardiaca.

Por lo tanto, repitiendo la exposición presentada al principio de esta sección, a pesar de los avances hechos en las terapias establecidas en este momento, todavía es necesario reducir la inaceptable carga de la insuficiencia cardiaca y se deben buscar nuevos enfoques adicionales para tratar y prevenir el avance de la enfermedad

Cuando se buscan nuevas terapias para la insuficiencia cardiaca, hay que considerar la fisiopatología subyacente del fallo cardiaco. Se ha observado durante mucho tiempo en el fallo cardiaco que la frecuencia cardiaca y la contractilidad se aumentan inicialmente con el fin de mantener el rendimiento cardiaco. A largo plazo, esta respuesta es finalmente perjudicial. Se reconoce, por ejemplo, que el aumento de la frecuencia cardiaca es un factor de riesgo para la mortalidad y morbilidad con consecuencias adversas en la función vascular, aterogénesis, isquemia miocárdica, consumo energético miocárdico y

función ventricular izquierda. Las taquiarritmias crónicas son una causa de la miocardiopatía reversible en seres humanos y se establece la estimulación auricular rápida como un modelo animal de miocardiopatía. En la insuficiencia cardíaca crónica, el exceso de estimulación adrenérgica señala respuestas biológicas adversas (incluyendo aumento de la frecuencia cardíaca) por los receptores β_1 , β_2 y α_2 en el miocardio.

En el fallo cardíaco, se busca el mantenimiento de la contracción ventricular adecuada, pero se produce a expensas del consumo de oxígeno y energía por el miocardio. La frecuencia cardíaca influye en dicha demanda de energía, de forma que una mayor frecuencia cardíaca requiere mayor gasto de energía. Por lo tanto, si se disminuyera la frecuencia cardíaca en pacientes con insuficiencia cardíaca, podría dar potencialmente como resultado una mayor eficacia energética.

Por lo tanto, se deduce que los fármacos que tienen la capacidad de reducir la frecuencia cardíaca pueden ser beneficiosos para tratar o prevenir la insuficiencia cardíaca. Para tratar el fallo cardíaco, una expresión que también se usa para indicar la insuficiencia cardíaca, el documento EP 0471388 (y su equivalente en EE.UU. la Patente de EE.UU. 5.516.773) sugiere el uso de un grupo específico de compuestos derivados de la estructura química básica de la benzazepina, y más específicamente el compuesto denominado zatebradina, [1-(7,8-dimetoxi-1,3,4,5-tetrahidro-2H-3-benzazepin-2-ona-3-il)-3-[N-metil-N-(2-(3,4-dimetoxi-fenil)-etil)-propano].

Estos derivados de benzazepina se describieron por primera vez en el documento EP 0065229, así como su capacidad para reducir la frecuencia cardíaca (efecto bradicárdico) actuando directamente en el nodo sinoauricular, y su capacidad para reducir la necesidad de oxígeno del corazón.

La zatebradina también se conoce del documento WO 01/78699 para tratar e inducir la regresión de la miocardiopatía hipertrófica (MCH) idiopática, miocardiopatía isquémica y enfermedades cardíacas hipertróficas valvulares.

Se han estudiado los efectos del agente bradicárdico zatebradina en un pequeño número de pacientes con insuficiencia cardíaca, no sometidos a terapia o estimulación auricular para inducir una taquicardia (Shinke et al., *Jpn. Circ. Journal*, 1999, Vol. 63, pp. 957-964) o comparado con el beta-bloqueador propranolol (Shinke et al., *Abstract Circ.*, 1997, Vol. 96, 1-644).

En el primero de los estudios, los autores concluyeron que el efecto de ahorro de oxígeno de la bradicardia debido al tratamiento con zatebradina podía ser beneficioso para el tratamiento de la insuficiencia cardíaca. En el

último estudio, la reducción de la frecuencia cardíaca comparable observada con la zatebradina y el beta-bloqueador, tuvo efectos favorables comparado con el pretratamiento. Sin embargo, hay que indicar que con el tratamiento de beta-bloqueador se conservó la eficacia cardíaca global, puesto que los beneficios de ahorro de energía de la reducción de la frecuencia cardíaca remedian el efecto negativo observado en la contractilidad. Los autores propusieron, que esto puede justificar la buena tolerancia de los beta-bloqueadores y la posible eficacia en la insuficiencia cardíaca. Sin embargo, el tratamiento con zatebradina mejoró la eficacia cardíaca ya que se produjo reducción de la frecuencia cardíaca, pero no acompañado del efecto adverso en la contractilidad.

Hay que señalar que estos dos estudios son pequeños y no intentan evaluar los beneficios de la administración crónica de zatebradina en las manifestaciones hemodinámicas o clínicas de la insuficiencia cardíaca. Además, las relaciones entre la reducción de la frecuencia cardíaca, función ventricular izquierda y prognosis en la insuficiencia cardíaca, son complejas. Sin embargo, existe una base científica de que la mejora del consumo energético cardíaco secundario a la reducción de la frecuencia cardíaca es un concepto importante en el tratamiento y prevención del avance de la insuficiencia cardíaca debida a la disfunción sistólica y/o diastólica (Laperche et al., *Heart* 1999, Vol. 81, pp. 336-341).

Otro grupo específico de compuestos derivados de un estructura química básica de amina cíclica, ha mostrado que también tiene valiosas propiedades bradicárdicas farmacológicas. Estos compuestos, el procedimiento para su preparación y composiciones farmacéuticas que los contienen, están descritos en el documento EP 0224794 y su equivalente de EE.UU. la patente de EE.UU. 5.175.157.

También se conoce uno de estos derivados de amina cíclica, la 3-[(N-(2-(3,4-dimetoxi-fenil)-etil)-piperidin-3-il)-metil]-7,8-dimetoxi-1,3,4,5-tetrahidro-2H-3-benzazepin-2-ona, y más particularmente su enantiómero S-(+) llamado cilobradina, la [(+)-3-[(N-(2-(3,4-dimetoxi-fenil)-etil)-piperidin-3-(S)-il)-metil]-7,8-dimetoxi-1,3,4,5-tetrahidro-2H-3-benzazepin-2-ona], del documento WO 01/78699, para tratar e inducir la regresión de la miocardiopatía hipertrófica (MCH) idiopática, miocardiopatía isquémica y enfermedades cardíacas hipertróficas valvulares.

Sin embargo, estos derivados de amina cíclica, y más específicamente la cilobradina, no se han sugerido para tratar o prevenir la insuficiencia

cardíaca.

Estudios científicos llevados a cabo con zatebradina y cilobradina con el fin de determinar el mecanismo de acción de estas sustancias bradicárdicas, han mostrado que tanto la zatebradina como la cilobradina bloquean selectivamente los canales de corriente catiónica modulados por cAMP y activados por hiperpolarización (HCN) en el tejido conductor del corazón, siendo los canales responsables de la corriente transmembranal conocidos como I_f . Se supone que es a través del bloqueo de esta corriente como la zatebradina y la cilobradina producen su efecto bradicárdico específico.

Sin embargo, los canales HCN están ampliamente distribuidos en el sistema nervioso, y en el ojo median la corriente conocida como I_h . También se ha investigado el efecto de la zatebradina y la cilobradina en el canal I_h (*Neuroscience*, Vol. 59(2), pp. 363-373, 1994 para zatebradina, y *British Journal of Pharmacology*, Vol. 125, pp. 741-750, 1998 para cilobradina). Los resultados han sugerido que aunque el canal I_h también puede ser bloqueado por estos compuestos, la interacción con los canales es algo diferente para ambos tejidos. Puesto que la I_h se ha descrito en las diferentes neuronas del sistema de procesamiento de señales visuales, se ha sugerido que el efecto sobre la corriente I_h es una explicación de los efectos secundarios (trastornos visuales) observados en pacientes tratados con bloqueadores I_f .

Se han llevado a cabo estudios adicionales usando respuestas de electroretinograma (ERG) registradas de ojos de gatos y mediciones psicofísicas llevadas a cabo en sujetos humanos voluntarios, en condiciones normales y después de administrar zatebradina (*Archives Italiennes de Biologie*, vol. 137, pp. 299-309, 1999, y *Vision Research*, vol. 39, pp. 1767-1774, 1999). Los resultados de estos estudios han mostrado que la zatebradina reduce la amplitud de la respuesta a estímulos de frecuencia por encima de 1 Hz, como muestran los registros del ERG. Además, la medición de las características de atenuación y de fase del primer armónico construido representando la amplitud de la respuesta y la fase en función de la frecuencia temporal de los estímulos en condiciones testigo y después de administración por inyección intravenosa o por vía oral de zatebradina, han mostrado que el efecto principal de la zatebradina bloqueadora del canal I_h es disminuir la amplitud de la respuesta a estímulos en el intervalo de frecuencia de 2 a 15 Hertzios, introduciendo un corte de exclusión en el paso de banda a aproximadamente 2 Hertzios.

Para confirmar estos supuestos, se han llevado a cabo estudios

recientes usando registros de electroretinograma (ERG) intraretiniano y vítreo en retina de gato intacta adaptada a la oscuridad (*Visual Neuroscience*, vol. 18(3), pp. 353-363, 2001). Estos estudios comparaban los cambios en la fase de recuperación después de las ondas a y b inducidas por una exposición a destellos brillantes de luz blanca difusa, después de inyecciones intraretinianas de sustancias que se sabe que bloquean las respuestas de las células bipolares y horizontales, o de sustancias que se sabe que bloquean el canal I_h . Los autores de este estudio han concluido que los bloqueadores del canal I_h reducen la fase de recuperación después de las ondas a inducidas por la exposición a la luz.

SUMARIO DE LA INVENCION

A partir de los resultados de los estudios científicos recientemente publicados sobre el mecanismo de acción de las sustancias bradicárdicas, que se han discutido en la sección previa, se esperaría una ventaja de la cilobradina frente a la zatebradina en el tratamiento de trastornos cardíacos tales como la insuficiencia cardíaca.

Sin embargo, como se discutirá a continuación, se ha encontrado sorprendentemente que la cilobradina presenta una ventaja frente a la zatebradina no sólo en términos de su duración de acción farmacológicamente más larga y la potencia de la dosis, sino lo que es más importante en su cardioselectividad, que da como resultado la disminución o ausencia de efectos secundarios visuales cuando se compara con dosis terapéuticas de la zatebradina.

Por lo tanto, un primer objetivo de la presente invención es que la cilobradina tiene propiedades farmacológicas intrínsecamente diferentes a la zatebradina, que permiten el bloqueo completo del canal de iones cardíaco con ausencia o disminución de efectos retinianos. Esta propiedad cardioselectiva inesperada representa una clara ventaja para la cilobradina frente, por ejemplo, a la zatebradina, para el tratamiento de enfermedades cardíacas tales como la insuficiencia cardíaca.

Un objetivo adicional de la presente invención es que la cilobradina es eficaz para tratar o prevenir la insuficiencia cardíaca de cualquier etiología, y por lo tanto puede reducir la mortalidad y morbilidad asociadas con la insuficiencia cardíaca de cualquier etiología.

Por lo tanto, la presente invención se dirige al uso de cilobradina, o sus sales farmacéuticamente aceptables, para tratar o prevenir la insuficiencia cardíaca de cualquier etiología.

La presente invención también es un método para tratar o prevenir la insuficiencia cardíaca de cualquier etiología, por administración a un paciente que lo necesite, de una composición farmacéutica que comprende cilobradina, o sus sales farmacéuticamente aceptables, junto con un vehículo farmacéuticamente aceptable.

DESCRIPCIÓN DE LAS REALIZACIONES PREFERIDAS

De acuerdo con una realización, la presente invención proporciona un nuevo uso del derivado de amina cíclica (+)-3-[(N-(2-(3,4-dimetoxi-fenil)-etil)-piperidin-3-(S)-il)-metil]-7,8-dimetoxi-1,3,4,5-tetrahidro-2H-3-benzazepin-2-ona, concretamente la cilobradina, o sus sales farmacéuticamente aceptables.

Para preparar la cilobradina o las sales farmacéuticamente aceptables de la cilobradina, se hace referencia al documento EP 0224794 o su equivalente en EE.UU. la patente de EE.UU. 5.175.157, que describen la síntesis química de estos compuestos.

De acuerdo con una realización adicional de la presente invención, entre las sales de cilobradina farmacéuticamente aceptables descritas en el documento EP 0224794 o su equivalente en EE.UU. la patente de EE.UU. 5.175.157, se prefieren las sales de hidrocloruro o hidrobromuro de cilobradina.

Más particularmente, la presente invención se dirige al uso de la cilobradina, o sus sales farmacéuticamente aceptables, para preparar una composición farmacéutica para tratar o prevenir la insuficiencia cardíaca de cualquier etiología.

De acuerdo con una realización adicional, la presente invención se dirige al uso de la cilobradina, o sus sales farmacéuticamente aceptables, para preparar una composición farmacéutica para prevenir la insuficiencia cardíaca de cualquier etiología.

De acuerdo con una realización adicional de la presente invención, el tratamiento o prevención de la insuficiencia cardíaca se puede evaluar por la capacidad del compuesto o composición farmacéutica de acuerdo con la presente invención, para reducir la mortalidad y morbilidad asociadas con la insuficiencia cardíaca de cualquier etiología.

De acuerdo con una realización adicional de la presente invención, el tratamiento o prevención de la insuficiencia cardíaca también comprende el tratamiento o prevención del fallo de corazón, fallo cardíaco, insuficiencia de corazón, fallo miocárdico, insuficiencia miocárdica, insuficiencia del músculo del corazón, insuficiencia del músculo cardíaco, gasto cardíaco insuficiente, debilidad del músculo del corazón, debilidad del músculo cardíaco, colapso

cardíaco, síncope cardíaco, insuficiencia cardíaca crónica, insuficiencia cardíaca aguda, descompensación del corazón, descompensación cardíaca, descompensación cardíaca, insuficiencia cardíaca diastólica, insuficiencia cardíaca del lado derecho, insuficiencia cardíaca sistólica, insuficiencia
5 cardíaca ventricular izquierda, insuficiencia cardíaca del lado izquierdo, insuficiencia cardíaca biventricular e insuficiencia cardíaca congestiva.

De acuerdo con una realización adicional de la presente invención, la insuficiencia cardíaca de cualquier etiología significa insuficiencia cardíaca diagnosticada como una consecuencia o complicación de cualquier otro
10 estado, enfermedad o trastorno, tal como por ejemplo, disfunción sistólica, disfunción diastólica, enfermedades cardíacas isquémicas, incluyendo infarto de miocardio, infarto ventricular derecho e isquemia crónica, enfermedades coronarias, hipertensión, hipertensión pulmonar primaria, hipertensión pulmonar secundaria, embolia pulmonar, estenosis arterial pulmonar,
15 enfermedad pulmonar obstructiva crónica, miocardiopatías restrictivas, miocardiopatías dilatadas debidas a razones infecciosas, tóxicas, metabólicas, familiares o desconocidas, miocarditis, anomalías congénitas, taquicardias e hipertrofia ventricular secundaria a trastornos genéticos o valvulares tales como insuficiencia de la válvula tricúspide, trastornos de la válvula mitral y/o
20 aórtica, infartos de corazón, enfermedades de tiroides y anemia.

De acuerdo con una realización adicional, para tratar o prevenir la insuficiencia cardíaca, también está dentro del alcance de la presente invención una combinación de cilobradina, o sus sales farmacéuticamente aceptables, con otras sustancias, tales como por ejemplo, diuréticos, glicósidos
25 cardíacos, inhibidores de la ECA (enzima convertidora de angiotensina), BRA (bloqueadores del receptor de angiotensina), vasodilatadores, beta-bloqueadores e inotropos, presentes en la misma composición farmacéutica, o dados como terapias separadas (llamada terapia adyuvante).

De acuerdo con una realización adicional de la presente invención, la
30 composición farmacéutica para usar de acuerdo con la presente invención, que comprende cilobradina o sus sales farmacéuticamente aceptables, sola o combinada con otras terapias para insuficiencia cardíaca incluyendo inhibidores de ECA, BRA, diuréticos o glicósidos cardíacos, se puede administrar a pacientes de cualquier forma médicamente aceptable.

35 De acuerdo con una realización adicional de la presente invención, la composición farmacéutica para usar de acuerdo con la presente invención, que comprende cilobradina o sus sales farmacéuticamente aceptables, se puede

- formular como formulación líquida o de polvos liofilizados para administración por vía oral o parenteral. Los polvos se pueden reconstituir por adición de un diluyente adecuado u otro vehículo farmacéuticamente aceptable antes de usarlos. La formulación líquida generalmente es una solución acuosa. Dicha
- 5 formulación es especialmente adecuada para administración por vía oral, pero también se puede usar para administración por vía parenteral, o contenida en un inhalador o nebulizador de dosis medidas para Insuflación. Puede ser conveniente añadir a la composición excipientes tales como polivinilpirrolidona o hidroxixelulosa.
- 10 De acuerdo con una realización adicional de la presente invención, la formulación líquida se puede administrar directamente por vía oral o cargada en una cápsula blanda.
- Alternativamente, los ingredientes se pueden encapsular, formar comprimidos o preparar en un jarabe para administración por vía oral. Se
- 15 pueden añadir vehículos sólidos o líquidos farmacéuticamente aceptables para potenciar o estabilizar la composición, o para facilitar la preparación de la composición. El vehículo también puede incluir un material de liberación sostenida.
- De acuerdo con otra realización de la presente invención, las
- 20 composiciones farmacéuticas se preparan siguiendo las técnicas convencionales de farmacia que implican, molienda, mezcla, granulación y compresión, cuando sea necesario, para formas de comprimidos, o molienda, mezcla y carga para formas de cápsulas.
- Para preparar composiciones farmacéuticas que comprenden
- 25 cilobradina o sus sales farmacéuticamente aceptables, se hace referencia en particular al documento EP 0224794 o su equivalente en EE.UU. la patente de EE.UU. 5.175.157 y al documento WO 01/78699, que describen ejemplos de formulaciones de cilobradina o sus sales farmacéuticamente aceptables inyectables, líquidas orales, en comprimidos, cápsulas y supositorios.
- 30 De acuerdo con una realización adicional de la presente invención, la formulación galénica preferida es un comprimido o una solución líquida para beber, aunque también están comprendidas dentro del alcance de la presente invención las formulaciones de la sustancia activa cilobradina o sus sales farmacéuticamente aceptables en cápsulas, supositorios e inyectables.
- 35 De acuerdo con una realización adicional de la presente invención, la composición farmacéutica que comprende el ingrediente activo cilobradina o sus sales farmacéuticamente aceptables, se puede administrar a animales así

como a seres humanos.

De acuerdo con una realización adicional de la presente invención, la composición farmacéutica que comprende el ingrediente activo cilobradina o sus sales farmacéuticamente aceptables, se administra preferiblemente
5 siguiendo un esquema de aplicación diario de una etapa o múltiples etapas.

De acuerdo con una realización adicional de la presente invención, cuando se administra para tratar o prevenir la insuficiencia cardíaca, se usa preferiblemente una dosis de 0,01 a 20 mg/kg de peso corporal de la sustancia activa cilobradina o sus sales farmacéuticamente aceptables, y ésta en una o
10 más aplicaciones diarias. Dentro de este intervalo, se prefieren más los siguientes intervalos de dosis: de 0,05 a 5 mg/kg de peso corporal, de 0,1 a 2,5 mg/kg de peso corporal, de 0,1 a 1 mg/kg de peso corporal, y de 0,1 a 0,75 mg/kg de peso corporal.

Ahora se describirá la invención con más detalle haciendo referencia a
15 los siguientes experimentos.

Como ya se ha mencionado antes, los estudios previos (publicados en *Archives Italiennes de Biologie*, vol. 137, pp. 299-309, 1999, y *Vision Research*, vol. 39, pp. 1767-1774, 1999) han establecido un modelo animal experimental para evaluar los efectos secundarios (problemas visuales) observados por
20 pacientes tratados con agentes bradicárdicos, tales como zatebradina. El contenido de estas referencias, y más particularmente las partes experimentales descritas en ellas, se incorporan aquí como referencia.

Estos estudios se basaron en una medición de las respuestas de electroretinogramas (ERG) registrados de ojos de gatos, en condiciones
25 normales y después de administrar zatebradina.

En el siguiente experimento se llevó a cabo el mismo experimento usando cilobradina, y los resultados se compararon con los resultados obtenidos con la zatebradina.

Con el fin de comparar los efectos secundarios visuales de ambos compuestos en condiciones en las que los fármacos son los más eficaces farmacológicamente en estos experimentos, tal como por ejemplo en la reducción de la frecuencia cardíaca, se eligió una dosis de 0,75 mg/kg de peso corporal para la cilobradina, y una dosis de 2,5 mg/kg de peso corporal para la zatebradina. Esta selección de la dosis se basa en el resultado mostrado en la
30 Figura 1, en la que se representa gráficamente la reducción de la frecuencia cardíaca frente a la dosis de fármaco aplicada (círculos blancos: zatebradina; círculos negros: cilobradina). Como puede verse en la Figura 1, con una dosis
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de 2,5 mg/kg de peso corporal, se obtiene una reducción de aproximadamente 44% de la frecuencia cardíaca con zatebradina (efecto máximo), y con una dosis de 0,75 mg/kg de peso corporal, se obtiene una reducción de aproximadamente 75% de la frecuencia cardíaca con cilobradina (también efecto máximo). Por lo tanto, eligiendo estas dosis, todavía se puede suponer que el efecto farmacológico sobre la frecuencia cardíaca de la cilobradina es mejor que el efecto farmacológico de la zatebradina.

En un experimento similar al experimento llevado a cabo por Gargini et al. (publicado en *Vision Research*, vol. 39, pp. 1767-1774, 1999), se evaluaron las características de atenuación y fase de la respuesta del ERG a luminancias moduladas sinusoidalmente, por representación gráfica de la amplitud de la respuesta a los estímulos de luz en función de la frecuencia temporal de los estímulos de luz. Los resultados de este experimento se muestran en la Figura 2, en la que los círculos blancos son las respuestas del testigo (no se ha inyectado sustancia activa), los círculos negros son las respuestas 15 minutos después de tratamiento con una dosis de zatebradina de 2,5 mg/kg de peso corporal (inyección i.v.), y los triángulos son las respuestas medidas 5 horas después de la inyección de zatebradina.

Los resultados confirman los resultados ya publicados por Gargini et al. (publicado en *Vision Research*, vol. 39, pp. 1767-1774, 1999), de que, con esta dosis, la zatebradina reduce la amplitud de la respuesta a estímulos de frecuencia por encima de 1 Hz y desplaza los correspondientes retardos de fase, como se muestra en los registros de ERG. Las mediciones llevadas a cabo después de 5 horas confirman que la respuesta visual vuelve a la normalidad después de 5 horas, y que el experimento no es destructivo para el sistema.

La Figura 3 muestra los resultados del mismo experimento llevado a cabo después de inyectar 0,75 mg/kg de peso corporal de cilobradina, en las mismas condiciones. Como es evidente a partir del resultado, no se puede detectar efecto visual con la cilobradina cuando se inyecta con una dosis eficaz para reducir la frecuencia cardíaca completamente.

A partir de estos resultados se concluye que una dosis de cilobradina que produce un efecto de saturación en la frecuencia cardíaca tiene consecuencias insignificantes en la respuesta visual. Esto demuestra la ventaja de la cilobradina frente a la zatebradina para producir un efecto farmacológico con menos efectos secundarios, y por lo tanto su superioridad para tratar la insuficiencia cardíaca.

Se realizó un experimento similar adicional para comparar el efecto secundario visual de la cilobradina y la zatebradina en estados en los que los fármacos son farmacológicamente eficaces en reducir la frecuencia cardíaca. El objetivo de este experimento fue comparar el efecto secundario visual de ambos fármacos en otro modelo animal experimental, concretamente sobre el sistema retinal de la rata. Además, el objetivo del experimento fue también comparar el efecto secundario visual de ambos fármacos en condiciones de tratamiento con los fármacos agudas y crónicas (más de dos semanas).

El principio de este experimento es nuevamente el mismo que el principio del experimento realizado por Gargini et al. y publicado en *Vision Research*, vol. 39, pp. 1767-1774, 1999.

Por tanto, este experimento se basó en una medida de las respuestas del electroretinograma (ERG) registradas en ratas pigmentadas anestesiadas en función de la frecuencia temporal de un estímulo luminoso oscilante aplicado. Los resultados del experimento se visualizan representando gráficamente la medida de la primera amplitud de la transformada de Fourier del ERG en función de la frecuencia del estímulo aplicado (estímulo luminoso oscilante de altos valores de luminancia y contraste).

Las Figuras 4 a 7 muestran los resultados del experimento en diferentes condiciones de tratamiento.

La Figura 4 muestra los resultados del experimento en condiciones de control (cuadrados y círculos); en condiciones de tratamiento agudo con tres dosis diferentes de cilobradina (triángulos: 0,3 mg de cilobradina/kg de peso corporal; triángulos invertidos: 1 mg de cilobradina/kg de peso corporal; rombos: 3 mg de cilobradina/kg de peso corporal). Las medidas de ERG se hicieron 30 minutos después de la inyección del fármaco. La frecuencia del ritmo cardíaco medida fue:

	Control	400 latidos por minuto.
	Tratamiento con cilobradina 0,3 mg/kg	364 latidos por minuto.
30	Tratamiento con cilobradina 1 mg/kg	316 latidos por minuto.
	Tratamiento con cilobradina 3 mg/kg	270 latidos por minuto.

La Figura 5 muestra los resultados del experimento en condiciones de control (cuadrados y círculos) y en condiciones de tratamiento agudo con una dosis única de zatebradina de 3 mg/kg de peso corporal (círculos). La medida del ERG se hizo cada 30 minutos después de la inyección del fármaco. La frecuencia del ritmo cardíaco medida fue:

Control	428 latidos por minuto.
Tratamiento con zatebradina 3 mg/kg	333 latidos por minuto.

La Figura 6 muestra los resultados del experimento en condiciones de control (cuadrados) y en condiciones de tratamiento crónico con una sola dosis de cilobradina de 1 mg/kg de peso corporal administrada diariamente durante 2 semanas (círculos). La medida del ERG se hizo después del tratamiento de 2 semanas. La frecuencia del ritmo cardíaco medida fue:

10	Control	400 latidos por minuto.
	Tratamiento con cilobradina 1 mg/kg	260 latidos por minuto.

La Figura 7 muestra los resultados del experimento en condiciones de control (círculos) y en condiciones de tratamiento crónico con una dosis doble de zatebradina de 3 mg/kg de peso corporal administrada diariamente durante dos semanas (cuadrados). La medida del ERG se hizo después de un tratamiento de dos semanas. La frecuencia del ritmo cardíaco medida fue:

20	Control	350 latidos por minuto.
	Tratamiento con cilobradina 1 mg/kg	285 latidos por minuto.

De este experimento, se puede sacar la conclusión de que en el tratamiento agudo (resultados de las Figuras 4 y 5), a dosis para las cuales son efectivos ambos fármacos en reducir la frecuencia cardíaca (como se confirmó por los valores de la frecuencia del ritmo cardíaco medida), no se pudo detectar ningún efecto sobre el ERG con la cilobradina, mientras que se observó una reducción de la amplitud de la respuesta a los estímulos de frecuencia por encima de 1 Hz, y un desplazamiento en los retrasos de fase correspondientes con zatebradina.

Además, se pueden sacar las mismas conclusiones de los resultados obtenidos con el tratamiento crónico durante dos semanas, como se puede ver cuando se comparan los resultados de las Figuras 6 y 7.

Este experimento realizado con ratas confirma los resultados previamente observados en gatos, según los cuales una dosis de cilobradina eficaz para reducir la frecuencia cardíaca tiene consecuencias despreciables sobre la respuesta visual. Esto también demuestra de nuevo la ventaja de la cilobradina sobre la zatebradina en producir un efecto farmacológico con

menos efectos secundarios, y por tanto, su superioridad para el tratamiento de la insuficiencia cardiaca.

Este experimento demuestra también que la cilobradina es eficaz en reducir la frecuencia cardiaca sin efectos secundarios visuales, y por tanto su aptitud en el tratamiento agudo, así como el tratamiento crónico de la insuficiencia cardiaca.

La invención también se describirá ahora con más detalle con referencia a los siguientes ejemplos de formulaciones de dosificación farmacéutica.

Por consiguiente, se han preparado formulaciones farmacéuticas para uso médico en seres humanos, que contienen entre 0,10 y 5 mg de sustancia activa. Más específicamente, las formulaciones de comprimidos para vía oral que han de emplearse en forma de una dosis única o múltiple en un esquema de aplicación diaria, y que contienen 0,25 mg, 0,5 mg, 1 mg ó 2 mg de sustancia activa, se han preparado como se describe en los siguientes ejemplos de formulación de comprimidos revestidos con películas.

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	Ejemplo 1	Ejemplo 2	Ejemplo 3	Ejemplo 4
	Dosis de 0,25 mg mg/comprimido revestido con película	Dosis de 0,5 mg mg/comprimido revestido con película	Dosis de 1 mg mg/comprimido revestido con película	Dosis de 2 mg mg/comprimido revestido con película
Núcleo:				
Cilobradina	0,27	0,54	1,08	2,16
Lactosa, monohidrato (Tabletoses)	56,42	56,15	82,28	164,56
Celulosa microcristalina, tipo 101	27,45	27,45	40,38	80,76
Carboximetilcelulosa (Ac-Di-Sol)	0,43	0,43	0,63	1,26
Estearato de magnesio (origen vegetal)	0,43	0,43	0,63	1,26

Peso del núcleo del comprimido:	85,00	85,00	125,00	250,00
Revestimiento:				
Hipromelosa (Methocel E5 Premium)	1,50	1,50	2,00	3,00
Macrogol 400	0,15	0,15	0,20	0,30
Dióxido de titanio	0,75	0,75	1,00	1,50
Talco	0,60	0,60	0,80	1,20
Peso del comprimido revestido con película	88,00	88,00	128,00	258,00

Estos comprimidos se pueden emplear para el tratamiento o prevención de la insuficiencia cardíaca como se ha definido en la presente invención.

REIVINDICACIONES

1. Uso de cilobradina o una de sus sales farmacéuticamente aceptable, para preparar una composición farmacéutica para tratar o prevenir la insuficiencia cardiaca.

2. Uso de acuerdo con la reivindicación 1, en el que la composición farmacéutica es para prevenir la insuficiencia cardiaca.

3. Uso de acuerdo con la reivindicación 1 ó 2, en el que la formulación galénica de la composición farmacéutica es un comprimido, una solución para beber, una cápsula, un supositorio o una formulación inyectable.

4. Uso de acuerdo con una cualquiera de las reivindicaciones 1 a 3, en el que la formulación galénica de la composición farmacéutica es un comprimido.

5. Uso de acuerdo con una cualquiera de las reivindicaciones 1 a 3, en el que la formulación galénica de la composición farmacéutica es una solución para beber.

6. Uso de acuerdo con una cualquiera de las reivindicaciones 1 a 5, en el que la composición farmacéutica se administra siguiendo un esquema de aplicación diario de una o múltiples etapas.

7. Uso de acuerdo con la reivindicación 6, en el que la dosis administrada de cilobradina o sus sales farmacéuticamente aceptables, está comprendida entre 0,01 y 20 mg/kg de peso corporal.

8. Uso de acuerdo con la reivindicación 6, en el que la dosis administrada de cilobradina o sus sales farmacéuticamente aceptables, está comprendida entre 0,05 y 5 mg/kg de peso corporal.

9. Uso de acuerdo con la reivindicación 6, en el que la dosis administrada de cilobradina o sus sales farmacéuticamente aceptables, está comprendida entre 0,1 y 2,5 mg/kg de peso corporal.

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10. Uso de acuerdo con la reivindicación 6, en el que la dosis administrada de cilobradina o sus sales farmacéuticamente aceptables, está comprendida entre 0,1 y 1 mg/kg de peso corporal.

5 11. Uso de acuerdo con la reivindicación 6, en el que la dosis administrada de cilobradina o sus sales farmacéuticamente aceptables, está comprendida entre 0,1 y 0,75 mg/kg de peso corporal.

10 12. Uso de acuerdo con una cualquiera de las reivindicaciones 1 a 11, en el que el tratamiento o prevención de la insuficiencia cardiaca se lleva a cabo combinado con otros agentes terapéuticos para tratar o prevenir la insuficiencia cardiaca, tales como diuréticos, glicósidos cardiacos, inhibidores de la ECA, BRA, vasodilatadores, beta-bloqueadores e inotropos.

15 13. Un método para tratar o prevenir la insuficiencia cardiaca, que comprende administrar a un paciente que lo necesite, una composición farmacéutica que comprende cilobradina o una de sus sales farmacéuticamente aceptable, junto con un vehículo farmacéuticamente aceptable.

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RESUMEN

La presente invención proporciona el uso en una composición farmacéutica de un derivado de amina cíclica específico, o sus sales farmacéuticamente aceptables, para tratar o prevenir la insuficiencia cardíaca de cualquier etiología.

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PRP/WPC13736/ID-000404

Fig. 1

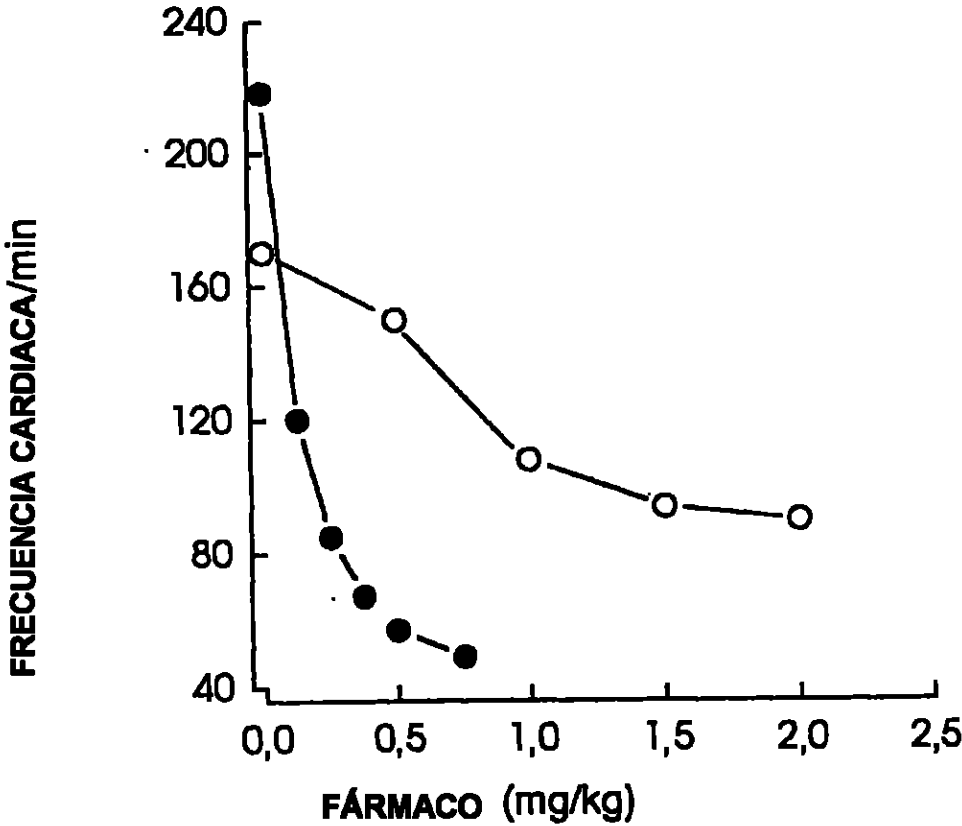


Fig. 2

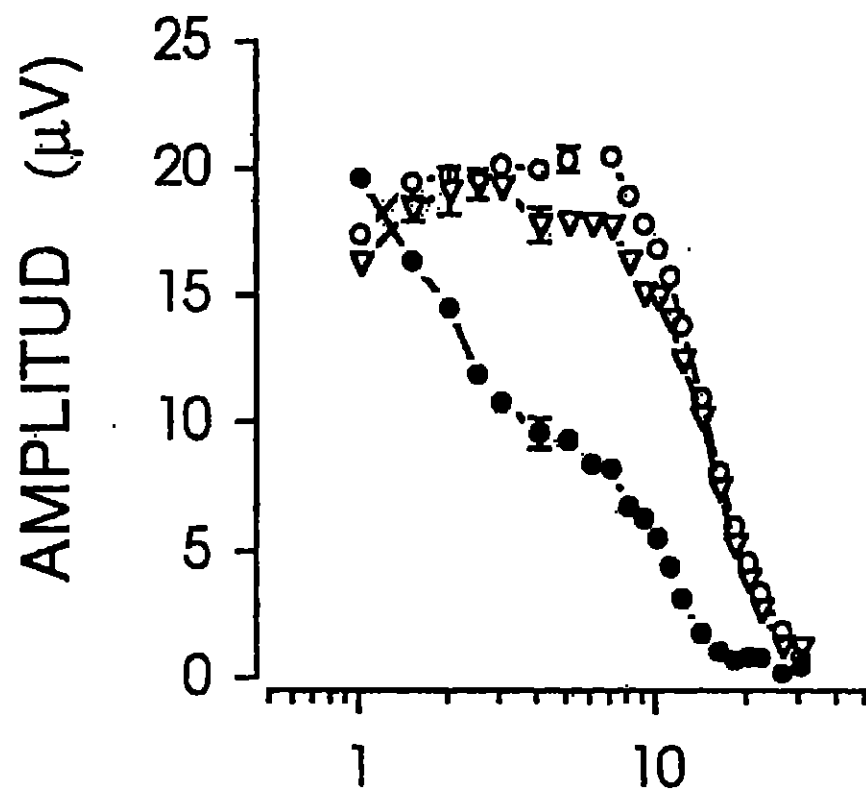


Fig. 3

104

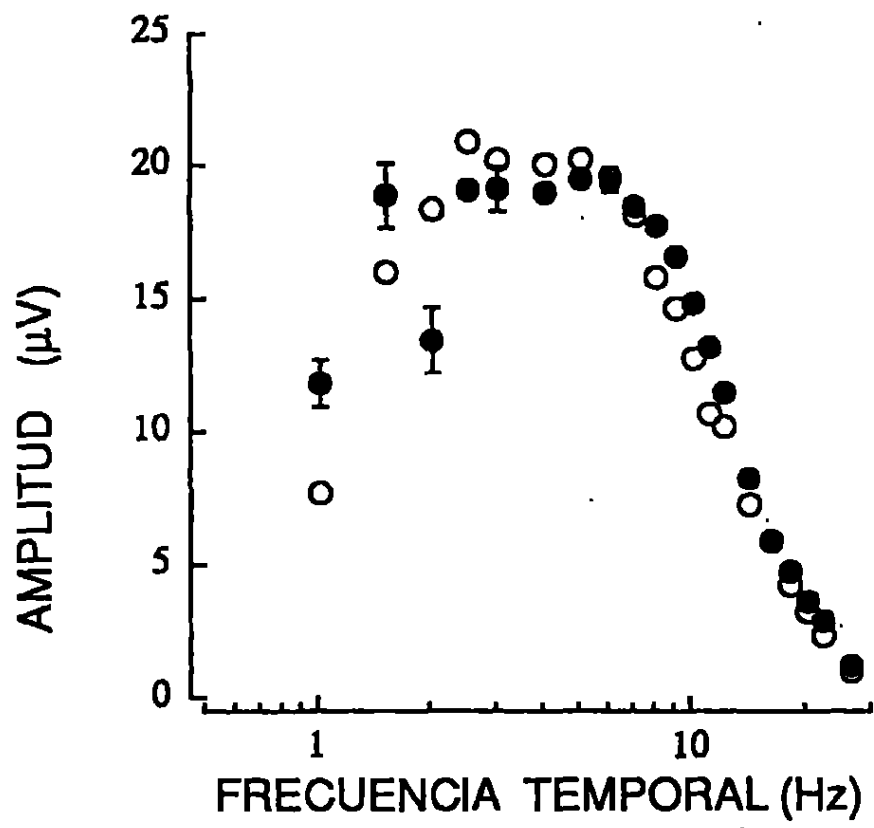


Fig. 4

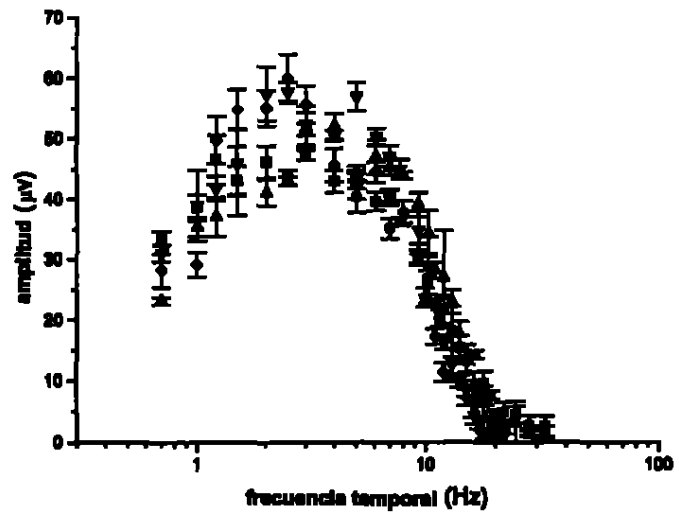


Fig. 5

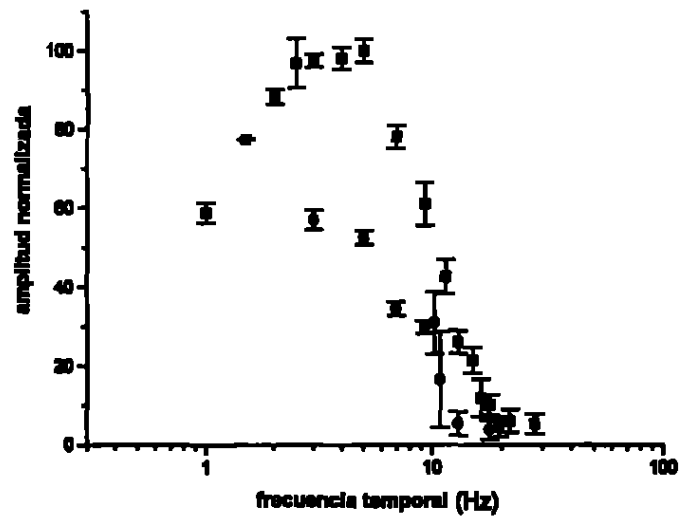
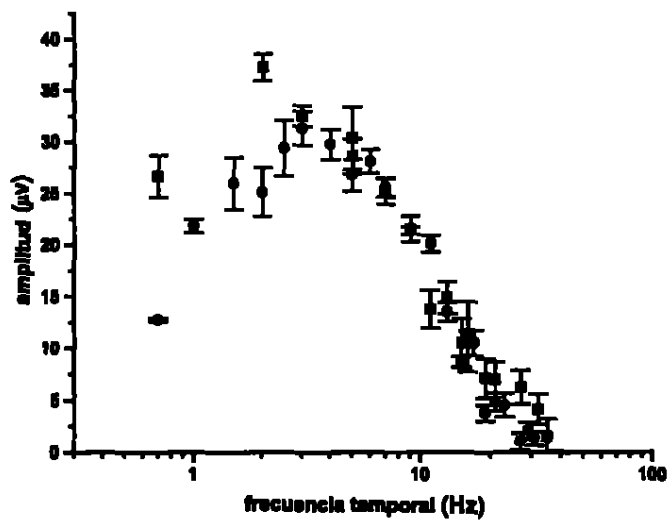
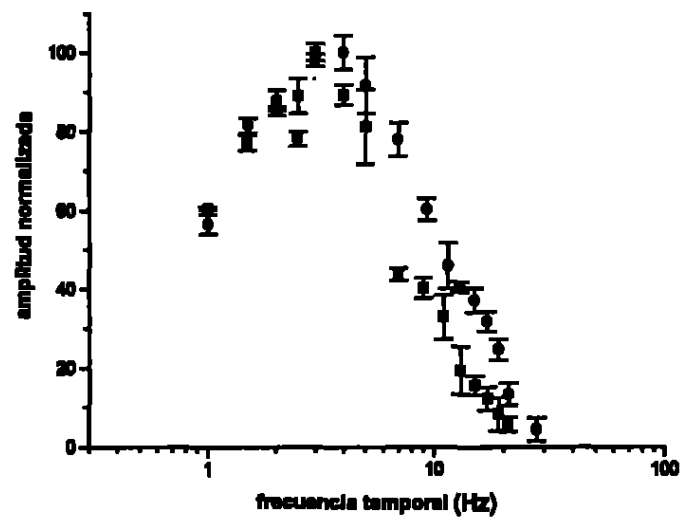


Fig. 6



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Fig. 7



REIVINDICACIONES MODIFICADAS (Colombia)

1. Una composición farmacéutica para el tratamiento o prevención de la falla cardíaca, que comprende cilobradina o una sal farmacéuticamente aceptable de la misma en una cantidad que permita un bloqueo completo de los canales iónicos cardíacos con ausencia o disminución de los efectos retinales, junto con un vehículo farmacéuticamente aceptable.

COLO 13736-841-057-7

PRP/WPC13736/ID-000428

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 05 - 3,794
FECHA : FEBRERO 7 DE 2005

SUPERINDUSTRIA Y COMERCIO
Radicacion : 05017675 00000000 Folios: 110
Fecha (AMB): 2005-02-24 17:02:19
Tramite : 011 PCT-PATENT 379 FASE INICI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

**** CONSIGNACION ****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PBO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	054-00110-1	3323/106	07/02/2005	22,990,000.00

**** CONCEPTO ****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	443,000.00
		TOTAL :	443,000.00

SOM: CUATROCIENTOS CUARENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Bo 13736-891-057-7

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

		USUARIO	RADICADOR
PATENTE DE INVENCION ✓	MODELO DE UTILIDAD	()	()
- Indicación de que se solicita la concesión de una patente.		()	()
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.		()	()
- Descripción de la invención.		()	()
- Dibujos de ser estos pertinentes.		()	()
- Comprobante de Pago de las tasas establecidas.		()	()
COMPLETA () ✓	INCOMPLETA ()	()	()
DISEÑO INDUSTRIAL ()			
- Indicación de que se solicita el registro de Diseño Industrial		()	()
- Datos de identificación del solicitante o de la persona que presenta la solicitud.		()	()
- Representación gráfica o fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.		()	()
- Comprobante de pago de las tasas establecidas		()	()
COMPLETA ()	INCOMPLETA ()	()	()
ESQUEMA DE TRAZADO ()			
- Indicación de que solicita el registro de un Esquema de trazado.		()	()
- Datos de identificación del solicitante o de la persona que presenta La solicitud.		()	()
- Representación gráfica del esquema de trazado		()	()
- Comprobante de pago de las tasas establecidas.		()	()
COMPLETA ()	INCOMPLETA ()	()	()

Firma Responsable:



Fecha:



Industria y Comercio
SUPERINTENDENCIA

Folio 112

2020
Bogotá, D.C.,

Doctor(a)
EMILIO FERRERO
Apoderado
BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG.

Oficio N°
- 12665

ASUNTO:	Radicación N°	05-17675
	Solicitud internacional	PCT/EP2003/007929
	Fecha inicio fase nacional	25/02/2005
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

- La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486).

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de fecha, 29 ABR 2005

Carrera 13 No. 27-00 Pisos 5, 7 y 10
Conmutador: 382 0840
Fax: 350 5220
E-mail: Info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia