



No. 06-101550- -00009-0000

Fecha: 2010-08-26 14:06:55 Dep. 2020 DIR.NUEVASCR
Tra. 2 PATENTES Eve: 1 REGDEPOSITO
Act. 608 MODIFICASOLICIT Folios: 21

FORMULARIO UNICO DE CORRECCIONES Y MODIFICACIONES
2000-10

SOLICITUD DE:

☐ Corrección de error material

☒ Modificación a una Solicitud

SOLICITANTE	Nombre:	LES LABORATOIRES SERVIER	IDENTIFICACION	
	Dirección:	12, PLACE DE LA DEFENSE 92415 COURBEVOIE CEDEX - FRANCE.	C.C. ☐	NIT ☐
	Teléfono:	01 55 72 60 00	Fax:	01 47 38 27 39
	E-Mail:		C.E. ☐	Otro ☐
	Domicilio:	FRANCIA	Número	_____
REPRESENTANTE O APODERADO	Nombre:	JULIO CÉSAR RAMÍREZ PIÑA	IDENTIFICACION	
	Dirección:	Carrera 11 N° 86 - 32 (oficina 101) Bogotá	C.C. ☒	NIT ☐
	Teléfono:	7420191-7420192	Fax:	530 09 58
	E-Mail:	<u>estrategia@estrategiajuridica.com</u>	C.E. ☐	Otro ☐
			Número	79.779.990 TP 113.206 CSJ

Número de Expediente: **06 101 550**

Descripción de la corrección o modificación solicitada:

Modificación de las reivindicaciones: Se desiste de las reivindicaciones 5 y 6 de la solicitud en trámite.

Comprobante de Pago No.: _____

Fecha _____

... **Anexos:**

☒ Comprobante de pago de la tasa.

☐ Poderes, si fuere el caso.

☐ Certificado de existencia y representación legal, si fuere el caso.

166

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 70,504
FECHA : AGOSTO 26 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
ALEXANDER BARRETO	CONSIGNACION	BANCO DE BOGOTA	062754387	353155073	20/08/2010	114,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-03	CAMBIO DE MODALIDAD Y MODIFICA	
		12 MARCAS Y LENAS COMERCIALES	114,000.00
		TOTAL :	\$ 114,000.00

SON: CIENTO CATORCE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Bogotá D.C., 26 de agosto de 2010.

Señores
DIRECCIÓN DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
Ministerio de Comercio, Industria y Turismo
E. S. D.

Expediente No.: **06 101 550**
Asunto: Contestación de requerimiento de fondo de la Patente:
"Forma cristalina delta d de clorhidrato de Ivabradina, su procedimiento de preparación y composiciones farmacéuticas que la contienen".
Solicitante: **LES LABORATOIRES SERVIER**

JULIO CÉSAR RAMÍREZ PIÑA, abogado en ejercicio, identificado con la cédula de ciudadanía número 79'779.990 de Bogotá, portador de la tarjeta profesional número 113.206 del C. S. de la J., domiciliado en esta ciudad en la carrera 11 No. 86 - 32 (oficina 101) de Bogotá, D.C., en mi condición de apoderado de la sociedad **LES LABORATOIRES SERVIER**, tal y como consta en el poder que obra en el expediente radicado el pasado 22 de octubre de 2009, por medio del presente escrito doy respuesta al requerimiento de fondo que obra en el Oficio 06856, fijado el 27 de mayo de 2010, en el siguiente sentido:

MOTIVOS Y DERECHO:

El Examinador pone en entredicho el nivel inventivo de la presente solicitud con base en ES 2 067 314. Estamos totalmente en desacuerdo con dicha afirmación.

El polimorfismo no es una propiedad inherente a todas las moléculas. Por ejemplo, la sacarosa se cristaliza en un solo sistema cristalino.

Aún no existe método alguno que permita predecir los polimorfos de un compuesto sólido con certeza significativa. La búsqueda de polimorfos es en gran medida un ejercicio empírico.

El (los) retículo(s) cristalino(s) específicos y el número de retículos de un polimorfo no son predecibles. Incluso si fuese posible predecir la existencia de polimorfos, no existe en la técnica una lección o sugerencia general que permita predecir la forma de hacer un polimorfo específico. No existe en la técnica una lección o sugerencia que permita identificar y apreciar las propiedades y las características de un polimorfo específico antes de que este sea identificado.

A efectos de obtener una forma polimórfica es preciso decidir lo que sigue:

- el solvente, de entre una serie de posibles solventes elegidos de entre:
 - solventes polares;
 - solventes no polares;
 - solventes hidrofílicos; y
 - solventes hidrofóbicos.
- la temperatura, de entre diversas temperaturas;
- el enfriamiento rápido de las soluciones;
- la adición opcional de un segundo solvente;
- la agitación vigorosa;
- el calentamiento;
- la sublimación;
- el cambio muy rápido del pH.

No basta saber que la cristalización es posible puesto que incluso en ese caso es preciso decidir las condiciones que deben emplearse de entre todas las condiciones mencionadas más arriba. Este es un programa de investigación.

Los condiciones halladas por el Solicitante para preparar la forma cristalina de la presente invención no fueron sugeridas por ES 2 067 314, que no revela la forma cristalina 8d del hidrocloreto de ivabradina ni sugiere que sea posible obtenerla ni la forma en que el individuo capacitado en la técnica puede proceder a fin de obtenerla.

Por tanto, el objeto de la presente invención es inventivo por sobre ES 2 067 314.

REIVINDICACIONES

Conforme al formulario de Modificaciones y Correcciones que se anexa, se eliminarán las reivindicaciones 5 y 6 de la presente solicitud.

ANEXO

Se aporta copia simple de la Patente Estadounidense No. 7,384,932 otorgada a favor de mi mandante.

NOTIFICACIONES

El suscrito recibirá notificaciones en la Carrera 11 No. 86 – 32 (Oficina 101) de la ciudad de Bogotá, D.C., o en el casillero asignado al suscrito por su Despacho.

Cordialmente,



JULIO CÉSAR RAMÍREZ PIÑA
CC No. 79'779.990 de Bogotá
T. P. No. 113.206 del C. S. de la J.



US007384932B2

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(12) **United States Patent**
Horvath et al.

(10) **Patent No.:** **US 7,384,932 B2**
(45) **Date of Patent:** **Jun. 10, 2008**

(54) **8D-CRYSTALLINE FORM OF IVABRADINE HYDROCHLORIDE, A PROCESS FOR ITS PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING IT**

FOREIGN PATENT DOCUMENTS

EP	0543859	3/1993
FR	2868777	10/2005

(75) Inventors: **Stephane Horvath**,
La-Chapelle-Saint-Mesmin (FR);
Marie-Noelle Auguste, Orleans (FR);
Gerard Damien, Meung-sur-Loire (FR)

OTHER PUBLICATIONS

"Ivabradine Hydrochloride Antianginal HCN (LF Current) Blocker". *Drugs of the Future*, pp. 652-658, 2003.

French Preliminary Search Report for FR0510354 of Jun. 26, 2006.
Ferrari, et al., *European Heart Journal Supplements*, 2005, 7 (Supplement H), H16-H21.

Fox, *European Heart Journal Supplements*, 2005, 7 (Supplement H), H33-H36.

(73) Assignee: **Les Laboratoires Servier**, Courbevoie Cedex (FR)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

Primary Examiner—Bruck Kifle

(74) Attorney, Agent, or Firm—Hueschen and Sage

(21) Appl. No.: 11/545,362

(22) Filed: **Oct. 10, 2006**

(57) **ABSTRACT**

(65) **Prior Publication Data**

US 2007/0082886 A1 Apr. 12, 2007

A 8d-crystalline form of ivabradine hydrochloride of formula (I):

(30) **Foreign Application Priority Data**

Oct. 11, 2005 (FR) 05 10354

(51) **Int. Cl.**

C07D 223/16 (2006.01)

A61K 31/55 (2006.01)

A61P 9/10 (2006.01)

(52) U.S. Cl. **514/212.07; 540/523**

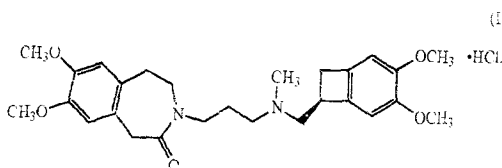
(58) **Field of Classification Search** **540/523;**
514/212.07

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,296,482 A 3/1994 Peglion et al.
2005 0228177 A1 10/2005 Lerestif et al.



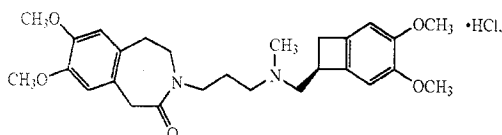
characterised by its powder X-ray diffraction data.

Medicinal products containing the same which are useful as bradycardics.

5 Claims, No Drawings

**δD-CRYSTALLINE FORM OF IVABRADINE
HYDROCHLORIDE, A PROCESS FOR ITS
PREPARATION AND PHARMACEUTICAL
COMPOSITIONS CONTAINING IT**

The present invention relates to the δd-crystalline form of ivabradine hydrochloride of formula (I)



to a process for its preparation and to pharmaceutical compositions containing it.

Ivabradine, and addition salts thereof with a pharmaceutically acceptable acid, and more especially its hydrochloride, have very valuable pharmacological and therapeutic properties, especially bradycardic properties, making those compounds useful in the treatment or prevention of various clinical situations of myocardial ischaemia such as angina pectoris, myocardial infarct and associated rhythm disturbances, and also in various pathologies involving rhythm disturbances, especially supraventricular rhythm disturbances, and in heart failure.

The preparation and therapeutic use of ivabradine and addition salts thereof with a pharmaceutically acceptable acid, and more especially its hydrochloride, have been described in the European patent specification EP 0 534 859.

In view of the pharmaceutical value of this compound, it has been of prime importance to obtain it with excellent purity. It has also been important to be able to synthesise it by means of a process that can readily be converted to the industrial scale, especially in a form that allows rapid filtration and drying. Finally, that form had to be perfectly reproducible, easily formulated and sufficiently stable to allow its storage for long periods without particular requirements for temperature, light or oxygen level.

The patent specification EP 0 534 859 describes a synthesis process for ivabradine and its hydrochloride. However, that document does not specify the conditions for obtaining ivabradine in a form that exhibits those characteristics in a reproducible manner.

The Applicant has now found that a particular salt of ivabradine, the hydrochloride, can be obtained in a well defined crystalline form that exhibits valuable characteristics for stability and processability.

More specifically, the present invention relates to the δd-crystalline form of ivabradine hydrochloride, characterised by the following powder X-ray diffraction diagram, measured using a PANalytical X'Pert Pro diffractometer together with an X'Celerator detector and expressed in terms of line position (Bragg's angle 2 theta, expressed in degrees), line height (expressed in counts), line area (expressed in counts x degrees), line width at half-height ("FWHM", expressed in degrees) and interplanar distance d (expressed in Å):

Line no.	Angle 2 theta (degrees)	Height (counts)	Area (counts x degrees)	FWHM (degrees)	Interplanar distance (Å)
1	4.1	414	41	0.1004	21.672
2	6.8	176	139	0.8029	13.078
3	8.6	1020	101	0.1004	10.305
4	9.1	323	43	0.1338	9.687
5	10.9	224	30	0.1338	8.100
6	11.7	354	47	0.1338	7.592
7	14.6	2774	458	0.1673	6.074
8	15.3	1805	328	0.184	5.800
9	16.6	986	163	0.1673	5.345
10	17.2	3821	946	0.2509	5.153
11	18.1	2290	378	0.1673	4.898
12	19.1	440	73	0.1673	4.649
13	19.6	289	38	0.1338	4.526
14	20.1	650	86	0.1338	4.408
15	20.9	887	146	0.1673	4.252
16	21.4	3112	565	0.184	4.147
17	22.1	1708	254	0.1506	4.027
18	22.5	1191	275	0.2342	3.945
19	23.4	619	102	0.1673	3.800
20	23.9	1343	222	0.1673	3.728
21	24.7	256	34	0.1338	3.604
22	25.6	309	41	0.1338	3.482
23	26.2	1899	313	0.1673	3.397
24	26.9	1588	183	0.1171	3.310
25	27.6	1357	224	0.1673	3.231
26	29.1	140	37	0.2676	3.069
27	29.5	145	29	0.2007	3.023

The invention relates also to a process for the preparation of the δd-crystalline form of ivabradine hydrochloride, which process is characterised in that acetonitrile or a mixture of acetonitrile and water is preheated, ivabradine hydrochloride is added, the solution obtained is allowed to cool at room temperature, held at room temperature until crystallisation is complete, and the crystals formed are dehydrated.

In the crystallisation process according to the invention it is possible to use ivabradine hydrochloride obtained by any process, for example ivabradine hydrochloride obtained by the preparation process described in patent specification EP 0 534 859.

The solution may advantageously be seeded during the cooling step.

The acetonitrile or mixture of acetonitrile and water is preferably preheated to a temperature between 60° C. and reflux, more preferably between 65 and 75° C.

The dilution is preferably more than 15 ml/g, more preferably between 50 and 100 ml/g.

The dehydration is preferably performed by heating.

The invention relates also to pharmaceutical compositions comprising as active ingredient the δd-crystalline form of ivabradine hydrochloride together with one or more appropriate, inert and non-toxic excipients. Among the pharmaceutical compositions according to the invention there may be mentioned, more especially, those that are suitable for oral, parenteral (intravenous or subcutaneous) or nasal administration, tablets or dragées, sublingual tablets, capsules, lozenges, suppositories, creams, ointments, dermal gels, injectable preparations and drinkable suspensions.

The useful dosage can be varied according to the nature and severity of the disorder, the administration route and the age and weight of the patient. The dosage varies from 1 to 500 mg per day in one or more administrations.

The Examples that follow illustrate the invention.

The X-ray powder diffraction spectrum was measured under the following experimental conditions:

PANalytical X'Pert Pro diffractometer, X'Celerator detector, temperature-regulated chamber,

voltage 45 kV, intensity 40 mA,

mounting θ - θ ,

nickel ($K\beta$) filter,

incident-beam and diffracted-beam Soller slit: 0.04 rad,

automatic divergence slits: irradiated length of 10 mm,

mask: 10 mm,

antiscatter slit: $\frac{1}{2}^\circ$,

measurement mode: continuous from 3° to 30° , in increments of 0.017° ,

measurement time per step : 19.7 s,

total time: 4 min 32 s,

measurement speed: $0.108^\circ/\text{s}$.

EXAMPLE 1

$\delta\delta$ -crystalline Form of Ivabradine Hydrochloride

160 ml of acetonitrile are preheated to 70°C , and then 2 g of ivabradine hydrochloride obtained according to the process described in patent specification EP 0 534 859 are added, in portions, with stirring until dissolution is complete. The solution is then stored at ambient temperature for 2 days. The crystals are removed by filtration in vacuo and are spread out onto a crystallisation plate. The crystals are then heated to a temperature of 85°C , at a rate of $10^\circ\text{C}/\text{min}$ and held at 85°C for 4 hours.

Powder X-ray Diffraction Diagram:

The powder X-ray diffraction profile (diffraction angles) of the $\delta\delta$ -form of ivabradine hydrochloride is given by the significant lines collated in the following table:

Line no.	Angle 2 theta (degrees)	Height (counts)	Area (counts x degrees)	FWHM (degrees)	Interplanar distance (Å)
1	4.1	414	41	0.1004	21.672
2	6.8	176	139	0.8029	13.078
3	8.6	1020	101	0.1004	10.305
4	9.1	323	43	0.1338	9.687
5	10.9	224	30	0.1338	8.100
6	11.7	354	47	0.1338	7.592
7	14.6	2774	458	0.1673	6.074
8	15.3	1805	328	0.184	5.800
9	16.6	986	163	0.1673	5.345
10	17.2	3821	946	0.2509	5.153
11	18.1	2290	378	0.1673	4.898
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24	26.9	1588	183	0.1171	3.310
25	27.6	1357	224	0.1673	3.231
26	29.1	140	37	0.2676	3.069
27	29.5	145	29	0.2007	3.023

EXAMPLE 2

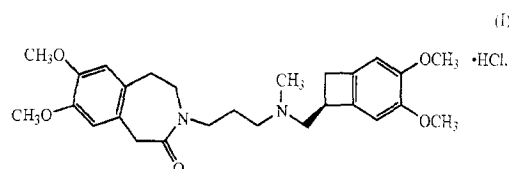
Pharmaceutical Composition

Formula for the preparation of 1000 tablets each containing 5 mg of ivabradine base:

Compound of Example 1	5.39 g
Maize starch	20 g
Anhydrous colloidal silica	0.2 g
Mannitol	63.91 g
PVP	10 g
Magnesium stearate	0.5 g

The invention claimed is:

1. A $\delta\delta$ -crystalline form of ivabradine hydrochloride of formula (I):



exhibiting essentially the following powder X-ray diffraction data, measured using a PANalytical X'Pert Pro diffractometer together with an X'Celerator detector and expressed in terms of line position (Bragg's angle 2 theta, expressed in degrees), line height (expressed in counts), line area (expressed in counts x degrees), line width at half-height ("FWHM", expressed in degrees) and interplanar distance d (expressed in Å):

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25	27.6	1357	224	0.1673	3.231
26	29.1	140	37	0.2676	3.069
27	29.5	145	29	0.2007	3.023

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2. A process for the preparation of the $\delta\delta$ -crystalline form of ivabradine hydrochloride of claim 1, wherein acetonitrile or a mixture of acetonitrile and water is preheated, ivabradine hydrochloride is added, the solution obtained is allowed to cool at room temperature, held at room temperature until crystallization is complete, and the crystals formed are dehydrated.

3. The process of claim 2, wherein the solution of ivabradine hydrochloride is seeded during the cooling step.

4. A solid pharmaceutical composition comprising as active ingredient the $\delta\delta$ -crystalline form of ivabradine

6

hydrochloride of claim 1, in combination with one or more pharmaceutically acceptable, inert, non-toxic carriers.

5. A method for treating a condition selected from angina pectoris, myocardial infarct and heart failure, such method comprising the step of administering to a living animal body, including a human, a therapeutically effective amount of $\delta\delta$ -crystalline form of ivabradine hydrochloride of claim 1.

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US007384932B2

(12) **United States Patent**
Horvath et al.

(10) **Patent No.:** **US 7,384,932 B2**
(45) **Date of Patent:** **Jun. 10, 2008**

(54) **δD-CRYSTALLINE FORM OF IVABRADINE
HYDROCHLORIDE, A PROCESS FOR ITS
PREPARATION AND PHARMACEUTICAL
COMPOSITIONS CONTAINING IT**

FOREIGN PATENT DOCUMENTS

EP	0543859	3/1993
FR	2868777	10/2005

(75) Inventors: **Stephane Horvath**,
La-Chapelle-Saint-Mesmin (FR);
Marie-Noelle Auguste, Orleans (FR);
Gerard Damien, Meung-sur-Loire (FR)

(73) Assignee: **Les Laboratoires Servier**, Courbevoie
Cedex (FR)

(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.

(21) Appl. No.: **11/545,362**

(22) Filed: **Oct. 10, 2006**

(65) Prior Publication Data

US 2007/0082886 A1 Apr. 12, 2007

(30) Foreign Application Priority Data

Oct. 11, 2005 (FR) 05 10354

(51) **Int. Cl.**
C07D 223/16 (2006.01)
A61K 31/55 (2006.01)
A61P 9/10 (2006.01)

(52) **U.S. Cl.** **514/212.07; 540/523**

(58) **Field of Classification Search** **540/523;**
514/212.07

See application file for complete search history.

(56) References Cited**U.S. PATENT DOCUMENTS**

5,296,482 A 3/1994 Peglion et al.
2005/0228177 A1 10/2005 Lerestif et al.

OTHER PUBLICATIONS

"Ivabradine Hydrochloride Antianginal HCN (LF Current)
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French Preliminary Search Report for FR0510354 of Jun. 26, 2006.
Ferrari, et al., *European Heart Journal Supplements*, 2005, 7
(Supplement H), H16-H21.

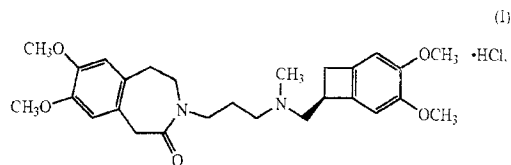
Fox, *European Heart Journal Supplements*, 2005, 7 (Supplement
H), H33-H36.

Primary Examiner—Bruck Kifle

(74) *Attorney, Agent, or Firm*—Hueschen and Sage

(57) ABSTRACT

A δd-crystalline form of ivabradine hydrochloride of formula (I):



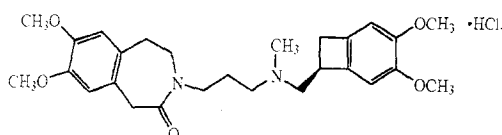
characterised by its powder X-ray diffraction data.

Medicinal products containing the same which are useful as
bradycardics.

5 Claims, No Drawings

**δD-CRYSTALLINE FORM OF IVABRADINE
HYDROCHLORIDE, A PROCESS FOR ITS
PREPARATION AND PHARMACEUTICAL
COMPOSITIONS CONTAINING IT**

The present invention relates to the δd-crystalline form of ivabradine hydrochloride of formula (I)



to a process for its preparation and to pharmaceutical compositions containing it.

Ivabradine, and addition salts thereof with a pharmaceutically acceptable acid, and more especially its hydrochloride, have very valuable pharmacological and therapeutic properties, especially bradycardic properties, making those compounds useful in the treatment or prevention of various clinical situations of myocardial ischaemia such as angina pectoris, myocardial infarct and associated rhythm disturbances, and also in various pathologies involving rhythm disturbances, especially supraventricular rhythm disturbances, and in heart failure.

The preparation and therapeutic use of ivabradine and addition salts thereof with a pharmaceutically acceptable acid, and more especially its hydrochloride, have been described in the European patent specification EP 0 534 859.

In view of the pharmaceutical value of this compound, it has been of prime importance to obtain it with excellent purity. It has also been important to be able to synthesise it by means of a process that can readily be converted to the industrial scale, especially in a form that allows rapid filtration and drying. Finally, that form had to be perfectly reproducible, easily formulated and sufficiently stable to allow its storage for long periods without particular requirements for temperature, light or oxygen level.

The patent specification EP 0 534 859 describes a synthesis process for ivabradine and its hydrochloride. However, that document does not specify the conditions for obtaining ivabradine in a form that exhibits those characteristics in a reproducible manner.

The Applicant has now found that a particular salt of ivabradine, the hydrochloride, can be obtained in a well defined crystalline form that exhibits valuable characteristics for stability and processability.

More specifically, the present invention relates to the δd-crystalline form of ivabradine hydrochloride, characterised by the following powder X-ray diffraction diagram, measured using a PANalytical X'Pert Pro diffractometer together with an X'Celerator detector and expressed in terms of line position (Bragg's angle 2 theta, expressed in degrees), line height (expressed in counts), line area (expressed in counts x degrees), line width at half-height ("FWHM", expressed in degrees) and interplanar distance d (expressed in Å):

Line no.	Angle 2 theta (degrees)	Height (counts)	Area (counts x degrees)	FWHM (degrees)	Interplanar distance (Å)
1	4.1	414	41	0.1004	21.672
2	6.8	176	139	0.8029	13.078
3	8.6	1020	101	0.1004	10.305
4	9.1	323	43	0.1338	9.687
5	10.9	224	30	0.1338	8.100
6	11.7	354	47	0.1338	7.592
7	14.6	2774	458	0.1673	6.074
8	15.3	1805	328	0.184	5.800
9	16.6	986	163	0.1673	5.345
10	17.2	3821	946	0.2509	5.155
11	18.1	2290	378	0.1673	4.898
12	19.1	440	73	0.1673	4.649
13	19.6	289	38	0.1338	4.526
14	20.1	650	86	0.1338	4.408
15	20.9	887	146	0.1673	4.252
16	21.4	3112	565	0.184	4.147
17	22.1	1708	254	0.1506	4.027
18	22.5	1191	275	0.2342	3.945
19	23.4	619	102	0.1673	3.800
20	23.9	1343	222	0.1673	3.728
21	24.7	256	34	0.1338	3.604
22	25.6	309	41	0.1338	3.482
23	26.2	1899	313	0.1673	3.397
24	26.9	1588	183	0.1171	3.310
25	27.6	1357	224	0.1673	3.231
26	29.1	140	37	0.2676	3.069
27	29.5	145	29	0.2007	3.023

The invention relates also to a process for the preparation of the δd-crystalline form of ivabradine hydrochloride, which process is characterised in that acetonitrile or a mixture of acetonitrile and water is preheated, ivabradine hydrochloride is added, the solution obtained is allowed to cool at room temperature, held at room temperature until crystallisation is complete, and the crystals formed are dehydrated.

In the crystallisation process according to the invention it is possible to use ivabradine hydrochloride obtained by any process, for example ivabradine hydrochloride obtained by the preparation process described in patent specification EP 0 534 859.

The solution may advantageously be seeded during the cooling step.

The acetonitrile or mixture of acetonitrile and water is preferably preheated to a temperature between 60° C. and reflux, more preferably between 65 and 75° C.

The dilution is preferably more than 15 ml/g, more preferably between 50 and 100 ml/g.

The dehydration is preferably performed by heating.

The invention relates also to pharmaceutical compositions comprising as active ingredient the δd-crystalline form of ivabradine hydrochloride together with one or more appropriate, inert and non-toxic excipients. Among the pharmaceutical compositions according to the invention there may be mentioned, more especially, those that are suitable for oral, parenteral (intravenous or subcutaneous) or nasal administration, tablets or dragées, sublingual tablets, capsules, lozenges, suppositories, creams, ointments, dermal gels, injectable preparations and drinkable suspensions.

The useful dosage can be varied according to the nature and severity of the disorder, the administration route and the age and weight of the patient. The dosage varies from 1 to 500 mg per day in one or more administrations.

The Examples that follow illustrate the invention.

The X-ray powder diffraction spectrum was measured under the following experimental conditions:

PANalytical X'Pert Pro diffractometer, X'Celerator detector, temperature-regulated chamber,

voltage 45 kV, intensity 40 mA,

mounting θ - θ ,

nickel ($K\beta$) filter,

incident-beam and diffracted-beam Soller slit: 0.04 rad,

automatic divergence slits: irradiated length of 10 mm,

mask: 10 mm,

antiscatter slit: $\frac{1}{2}^\circ$,

measurement mode: continuous from 3° to 30° , in increments of 0.017° ,

measurement time per step: 19.7 s,

total time: 4 min 32 s,

measurement speed: $0.108^\circ/\text{s}$.

EXAMPLE 1

δ d-crystalline Form of Ivabradine Hydrochloride

160 ml of acetonitrile are preheated to 70°C . and then 2 g of ivabradine hydrochloride obtained according to the process described in patent specification EP 0 534 859 are added, in portions, with stirring until dissolution is complete. The solution is then stored at ambient temperature for 2 days. The crystals are removed by filtration in vacuo and are spread out onto a crystallisation plate. The crystals are then heated to a temperature of 85°C . at a rate of $10^\circ\text{C}/\text{min}$ and held at 85°C . for 4 hours.

Powder X-ray Diffraction Diagram:

The powder X-ray diffraction profile (diffraction angles) of the δ d-form of ivabradine hydrochloride is given by the significant lines collated in the following table:

Line no.	Angle 2 theta (degrees)	Height (counts)	Area (counts $\times$ degrees)	FWHM (degrees)	Interplanar distance (Å)
1	4.1	414	41	0.1004	21.672
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11	18.1	2290	378	0.1673	4.898
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13	19.6	289	38	0.1338	4.526
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17	22.1	1708	254	0.1506	4.027
18	22.5	1191	275	0.2342	3.945
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20	23.9	1343	222	0.1673	3.728
21	24.7	256	34	0.1338	3.604
22	25.6	309	41	0.1338	3.482
23	26.2	1899	313	0.1673	3.397
24	26.9	1588	183	0.1171	3.310
25	27.6	1357	224	0.1673	3.231
26	29.1	140	37	0.2676	3.069
27	29.5	145	29	0.2007	3.023

EXAMPLE 2

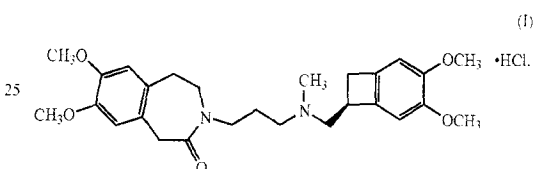
Pharmaceutical Composition

Formula for the preparation of 1000 tablets each containing 5 mg of ivabradine base:

Compound of Example 1	5.39 g
Maize starch	20 g
Anhydrous colloidal silica	0.2 g
Mannitol	63.91 g
PVP	10 g
Magnesium stearate	0.5 g

The invention claimed is:

1. A δ d-crystalline form of ivabradine hydrochloride of formula (I):



exhibiting essentially the following powder X-ray diffraction data, measured using a PANalytical X'Pert Pro diffractometer together with an X'Celerator detector and expressed in terms of line position (Bragg's angle 2 theta, expressed in degrees), line height (expressed in counts), line area (expressed in counts $\times$ degrees), line width at half-height ("FWHM", expressed in degrees) and interplanar distance d (expressed in Å):

Line no.	Angle 2 theta (degrees)	Height (counts)	Area (counts $\times$ degrees)	FWHM (degrees)	Interplanar distance (Å)
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25	27.6	1357	224	0.1673	3.231
26	29.1	140	37	0.2676	3.069
27	29.5	145	29	0.2007	3.023

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2. A process for the preparation of the δ d-crystalline form of ivabradine hydrochloride of claim 1, wherein acetonitrile or a mixture of acetonitrile and water is preheated, ivabradine hydrochloride is added, the solution obtained is allowed to cool at room temperature, held at room temperature until crystallization is complete, and the crystals formed are dehydrated.

3. The process of claim 2, wherein the solution of ivabradine hydrochloride is seeded during the cooling step.

4. A solid pharmaceutical composition comprising as active ingredient the δ d-crystalline form of ivabradine

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hydrochloride of claim 1, in combination with one or more pharmaceutically acceptable, inert, non-toxic carriers.

5. A method for treating a condition selected from angina pectoris, myocardial infarct and heart failure, such method comprising the step of administering to a living animal body, including a human, a therapeutically effective amount of δ d-crystalline form of ivabradine hydrochloride of claim 1.

* * * * *



US007384932B2

(12) **United States Patent**
Horvath et al.

(10) **Patent No.:** **US 7,384,932 B2**
(45) **Date of Patent:** **Jun. 10, 2008**

(54) **δD-CRYSTALLINE FORM OF IVABRADINE
HYDROCHLORIDE, A PROCESS FOR ITS
PREPARATION AND PHARMACEUTICAL
COMPOSITIONS CONTAINING IT**

FOREIGN PATENT DOCUMENTS

EP	0543859	3/1993
FR	2868777	10/2005

(75) Inventors: **Stephane Horvath**,
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(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.

(21) Appl. No.: **11/545,362**

(22) Filed: **Oct. 10, 2006**

(65) **Prior Publication Data**

US 2007/0082886 A1 Apr. 12, 2007

(30) **Foreign Application Priority Data**

Oct. 11, 2005 (FR) 05 10354

(51) **Int. Cl.**

C07D 223/16 (2006.01)

A61K 31/55 (2006.01)

A61P 9/10 (2006.01)

(52) U.S. Cl. **514/212.07; 540/523**

(58) **Field of Classification Search** **540/523;**
514/212.07

See application file for complete search history.

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French Preliminary Search Report for FR0510354 of Jun. 26, 2006.
Ferrari, et al., *European Heart Journal Supplements*, 2005, 7
(Supplement H), H16-H21.

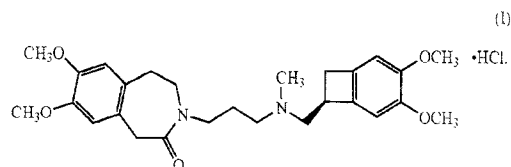
Fox, *European Heart Journal Supplements*, 2005, 7 (Supplement
H), H33-H36.

Primary Examiner—Bruck Kitle

(74) *Attorney, Agent, or Firm*—Hueschen and Sage

(57) **ABSTRACT**

A δd-crystalline form of ivabradine hydrochloride of formula (I):



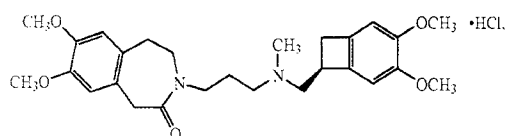
characterised by its powder X-ray diffraction data.

Medicinal products containing the same which are useful as
bradycardics.

5 Claims, No Drawings

**δD-CRYSTALLINE FORM OF IVABRADINE
HYDROCHLORIDE, A PROCESS FOR ITS
PREPARATION AND PHARMACEUTICAL
COMPOSITIONS CONTAINING IT**

The present invention relates to the δd-crystalline form of ivabradine hydrochloride of formula (I)



to a process for its preparation and to pharmaceutical compositions containing it.

Ivabradine, and addition salts thereof with a pharmaceutically acceptable acid, and more especially its hydrochloride, have very valuable pharmacological and therapeutic properties, especially bradycardic properties, making those compounds useful in the treatment or prevention of various clinical situations of myocardial ischaemia such as angina pectoris, myocardial infarct and associated rhythm disturbances, and also in various pathologies involving rhythm disturbances, especially supraventricular rhythm disturbances, and in heart failure.

The preparation and therapeutic use of ivabradine and addition salts thereof with a pharmaceutically acceptable acid, and more especially its hydrochloride, have been described in the European patent specification EP 0 534 859.

In view of the pharmaceutical value of this compound, it has been of prime importance to obtain it with excellent purity. It has also been important to be able to synthesise it by means of a process that can readily be converted to the industrial scale, especially in a form that allows rapid filtration and drying. Finally, that form had to be perfectly reproducible, easily formulated and sufficiently stable to allow its storage for long periods without particular requirements for temperature, light or oxygen level.

The patent specification EP 0 534 859 describes a synthesis process for ivabradine and its hydrochloride. However, that document does not specify the conditions for obtaining ivabradine in a form that exhibits those characteristics in a reproducible manner.

The Applicant has now found that a particular salt of ivabradine, the hydrochloride, can be obtained in a well defined crystalline form that exhibits valuable characteristics for stability and processability.

More specifically, the present invention relates to the δd-crystalline form of ivabradine hydrochloride, characterised by the following powder X-ray diffraction diagram, measured using a PANalytical X'Pert Pro diffractometer together with an X'Celerator detector and expressed in terms of line position (Bragg's angle 2 theta, expressed in degrees), line height (expressed in counts), line area (expressed in counts x degrees), line width at half-height ("FWHM", expressed in degrees) and interplanar distance d (expressed in Å):

Line no.	Angle 2 theta (degrees)	Height (counts)	Area (counts x degrees)	FWHM (degrees)	Interplanar distance (Å)
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2	6.8	176	139	0.8029	13.078
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4	9.1	323	43	0.1338	9.687
5	10.9	224	30	0.1338	8.100
6	11.7	354	47	0.1338	7.592
7	14.6	2774	458	0.1673	6.074
8	15.3	1805	328	0.184	5.800
9	16.6	986	163	0.1673	5.345
10	17.2	3821	946	0.2509	5.153
11	18.1	2290	378	0.1673	4.898
12	19.1	440	73	0.1673	4.649
13	19.6	289	38	0.1338	4.526
14	20.1	650	86	0.1338	4.408
15	20.9	887	146	0.1673	4.252
16	21.4	3112	565	0.184	4.147
17	22.1	1708	254	0.1506	4.027
18	22.5	1191	275	0.2342	3.945
19	23.4	619	102	0.1673	3.800
20	23.9	1343	222	0.1673	3.728
21	24.7	256	34	0.1338	3.604
22	25.6	309	41	0.1338	3.482
23	26.2	1899	313	0.1673	3.397
24	26.9	1588	183	0.1171	3.310
25	27.6	1357	224	0.1673	3.231
26	29.1	140	37	0.2676	3.069
27	29.5	145	29	0.2007	3.023

The invention relates also to a process for the preparation of the δd-crystalline form of ivabradine hydrochloride, which process is characterised in that acetonitrile or a mixture of acetonitrile and water is preheated, ivabradine hydrochloride is added, the solution obtained is allowed to cool at room temperature, held at room temperature until crystallisation is complete, and the crystals formed are dehydrated.

In the crystallisation process according to the invention it is possible to use ivabradine hydrochloride obtained by any process, for example ivabradine hydrochloride obtained by the preparation process described in patent specification EP 0 534 859.

The solution may advantageously be seeded during the cooling step.

The acetonitrile or mixture of acetonitrile and water is preferably preheated to a temperature between 60° C. and reflux, more preferably between 65 and 75° C.

The dilution is preferably more than 15 ml/g, more preferably between 50 and 100 ml/g.

The dehydration is preferably performed by heating.

The invention relates also to pharmaceutical compositions comprising as active ingredient the δd-crystalline form of ivabradine hydrochloride together with one or more appropriate, inert and non-toxic excipients. Among the pharmaceutical compositions according to the invention there may be mentioned, more especially, those that are suitable for oral, parenteral (intravenous or subcutaneous) or nasal administration, tablets or dragees, sublingual tablets, capsules, lozenges, suppositories, creams, ointments, dermal gels, injectable preparations and drinkable suspensions.

The useful dosage can be varied according to the nature and severity of the disorder, the administration route and the age and weight of the patient. The dosage varies from 1 to 500 mg per day in one or more administrations.

The Examples that follow illustrate the invention.

The X-ray powder diffraction spectrum was measured under the following experimental conditions:

PANalytical X'Pert Pro diffractometer, X'Celerator detector, temperature-regulated chamber, voltage 45 kV, intensity 40 mA, mounting θ - θ , nickel ($K\beta$) filter, incident-beam and diffracted-beam Soller slit: 0.04 rad, automatic divergence slits: irradiated length of 10 mm, mask: 10 mm, antiscatter slit: $\frac{1}{2}^\circ$.

measurement mode: continuous from 3° to 30° , in increments of 0.017° .

measurement time per step : 19.7 s.

total time: 4 min 32 s.

measurement speed: 0.108°/s.

EXAMPLE 1

δ -crystalline Form of Ivabradine Hydrochloride

160 ml of acetonitrile are preheated to 70°C . and then 2 g of ivabradine hydrochloride obtained according to the process described in patent specification EP 0 534 859 are added, in portions, with stirring until dissolution is complete. The solution is then stored at ambient temperature for 2 days. The crystals are removed by filtration in vacuo and are spread out onto a crystallisation plate. The crystals are then heated to a temperature of 85°C . at a rate of $10^\circ\text{C}/\text{min}$ and held at 85°C . for 4 hours.

Powder X-ray Diffraction Diagram:

The powder X-ray diffraction profile (diffraction angles) of the δ -form of ivabradine hydrochloride is given by the significant lines collated in the following table:

Line no.	Angle 2 theta (degrees)	Height (counts)	Area (counts x degrees)	FWHM (degrees)	Interplanar distance (Å)
1	4.1	414	41	0.1004	21.672
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25	27.6	1357	224	0.1673	3.231
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EXAMPLE 2

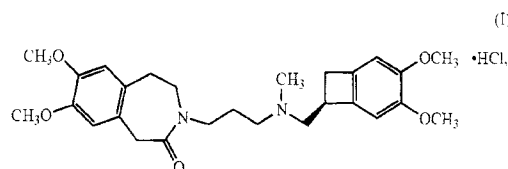
Pharmaceutical Composition

Formula for the preparation of 1000 tablets each containing 5 mg of ivabradine base:

Compound of Example 1	5.39 g
Maize starch	20 g
Anhydrous colloidal silica	0.2 g
Mannitol	63.91 g
PVP	10 g
Magnesium stearate	0.5 g

The invention claimed is:

1. A δ -crystalline form of ivabradine hydrochloride of formula (I):



exhibiting essentially the following powder X-ray diffraction data, measured using a PANalytical X'Pert Pro diffractometer together with an X'Celerator detector and expressed in terms of line position (Bragg's angle 2 theta, expressed in degrees), line height (expressed in counts), line area (expressed in counts x degrees), line width at half-height ("FWHM", expressed in degrees) and interplanar distance d (expressed in Å):

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25	27.6	1357	224	0.1673	3.231
26	29.1	140	37	0.2676	3.069
27	29.5	145	29	0.2007	3.023

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2. A process for the preparation of the $\delta\delta$ -crystalline form of ivabradine hydrochloride of claim 1, wherein acetonitrile or a mixture of acetonitrile and water is preheated, ivabradine hydrochloride is added, the solution obtained is allowed to cool at room temperature, held at room temperature until crystallization is complete, and the crystals formed are dehydrated.

3. The process of claim 2, wherein the solution of ivabradine hydrochloride is seeded during the cooling step.

4. A solid pharmaceutical composition comprising as active ingredient the $\delta\delta$ -crystalline form of ivabradine

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hydrochloride of claim 1, in combination with one or more pharmaceutically acceptable, inert, non-toxic carriers.

5. A method for treating a condition selected from angina pectoris, myocardial infarct and heart failure, such method comprising the step of administering to a living animal body, including a human, a therapeutically effective amount of $\delta\delta$ -crystalline form of ivabradine hydrochloride of claim 1.

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(12) **United States Patent**
Horvath et al.

(10) **Patent No.:** **US 7,384,932 B2**
(45) **Date of Patent:** **Jun. 10, 2008**

(54) **δ D-CRYSTALLINE FORM OF IVABRADINE HYDROCHLORIDE, A PROCESS FOR ITS PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING IT**

FOREIGN PATENT DOCUMENTS

EP	0543859	3/1993
FR	2868777	10/2005

(75) **Inventors:** **Stephane Horvath**,
La-Chapelle-Saint-Mesmin (FR);
Marie-Noelle Auguste, Orleans (FR);
Gerard Damien, Meung-sur-Loire (FR)

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Fox, *European Heart Journal Supplements*, 2005, 7 (Supplement H), H33-H36.

(73) **Assignee:** **Les Laboratoires Servier**, Courbevoie Cedex (FR)

(*) **Notice:** Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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(21) **Appl. No.:** **11/545,362**

(22) **Filed:** **Oct. 10, 2006**

(57) **ABSTRACT**

(65) **Prior Publication Data**

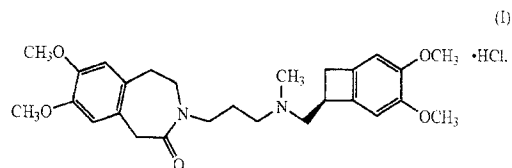
US 2007/0082886 A1 Apr. 12, 2007

(30) **Foreign Application Priority Data**

Oct. 11, 2005 (FR) 05 10354

A δ d-crystalline form of ivabradine hydrochloride of formula (I):

(51) **Int. Cl.**
C07D 223/16 (2006.01)
A61K 31/55 (2006.01)
A61P 9/10 (2006.01)



(52) **U.S. Cl.** **514/212.07; 540/523**

(58) **Field of Classification Search** **540/523; 514/212.07**

See application file for complete search history.

characterised by its powder X-ray diffraction data.

(56) **References Cited**

U.S. PATENT DOCUMENTS

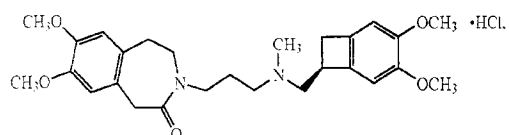
5,296,482 A 3 1994 Peglion et al.
2005.0228177 A1 10 2005 Lerestif et al.

Medicinal products containing the same which are useful as bradycardics.

5 Claims, No Drawings

**δD-CRYSTALLINE FORM OF IVABRADINE
HYDROCHLORIDE, A PROCESS FOR ITS
PREPARATION AND PHARMACEUTICAL
COMPOSITIONS CONTAINING IT**

The present invention relates to the δd-crystalline form of ivabradine hydrochloride of formula (I)



to a process for its preparation and to pharmaceutical compositions containing it.

Ivabradine, and addition salts thereof with a pharmaceutically acceptable acid, and more especially its hydrochloride, have very valuable pharmacological and therapeutic properties, especially bradycardic properties, making those compounds useful in the treatment or prevention of various clinical situations of myocardial ischaemia such as angina pectoris, myocardial infarct and associated rhythm disturbances, and also in various pathologies involving rhythm disturbances, especially supraventricular rhythm disturbances, and in heart failure.

The preparation and therapeutic use of ivabradine and addition salts thereof with a pharmaceutically acceptable acid, and more especially its hydrochloride, have been described in the European patent specification EP 0 534 859.

In view of the pharmaceutical value of this compound, it has been of prime importance to obtain it with excellent purity. It has also been important to be able to synthesise it by means of a process that can readily be converted to the industrial scale, especially in a form that allows rapid filtration and drying. Finally, that form had to be perfectly reproducible, easily formulated and sufficiently stable to allow its storage for long periods without particular requirements for temperature, light or oxygen level.

The patent specification EP 0 534 859 describes a synthesis process for ivabradine and its hydrochloride. However, that document does not specify the conditions for obtaining ivabradine in a form that exhibits those characteristics in a reproducible manner.

The Applicant has now found that a particular salt of ivabradine, the hydrochloride, can be obtained in a well defined crystalline form that exhibits valuable characteristics for stability and processability.

More specifically, the present invention relates to the δd-crystalline form of ivabradine hydrochloride, characterised by the following powder X-ray diffraction diagram, measured using a PANalytical X'Pert Pro diffractometer together with an X'Celerator detector and expressed in terms of line position (Bragg's angle 2 theta, expressed in degrees), line height (expressed in counts), line area (expressed in counts x degrees), line width at half-height ("FWHM", expressed in degrees) and interplanar distance d (expressed in Å):

Line no.	Angle 2 theta (degrees)	Height (counts)	Area (counts x degrees)	FWHM (degrees)	Interplanar distance (Å)
1	4.1	414	41	0.1004	21.672
2	6.8	176	139	0.8029	13.078
3	8.6	1020	101	0.1004	10.305
4	9.1	323	43	0.1338	9.687
5	10.9	224	30	0.1338	8.100
6	11.7	354	47	0.1338	7.592
7	14.6	2774	458	0.1673	6.074
8	15.3	1805	328	0.184	5.800
9	16.6	986	163	0.1673	5.345
10	17.2	3821	946	0.2509	5.153
11	18.1	2290	378	0.1673	4.898
12	19.1	440	73	0.1673	4.649
13	19.6	289	38	0.1338	4.526
14	20.1	650	86	0.1338	4.408
15	20.9	887	146	0.1673	4.252
16	21.4	3112	565	0.184	4.147
17	22.1	1708	254	0.1506	4.027
18	22.5	1191	275	0.2342	3.945
19	23.4	619	102	0.1673	3.800
20	23.9	1343	222	0.1673	3.728
21	24.7	256	34	0.1338	3.604
22	25.6	309	41	0.1338	3.482
23	26.2	1899	313	0.1673	3.397
24	26.9	1588	183	0.1171	3.310
25	27.6	1357	224	0.1673	3.231
26	29.1	140	37	0.2676	3.069
27	29.5	145	29	0.2007	3.023

The invention relates also to a process for the preparation of the δd-crystalline form of ivabradine hydrochloride, which process is characterised in that acetonitrile or a mixture of acetonitrile and water is preheated, ivabradine hydrochloride is added, the solution obtained is allowed to cool at room temperature, held at room temperature until crystallisation is complete, and the crystals formed are dehydrated.

In the crystallisation process according to the invention it is possible to use ivabradine hydrochloride obtained by any process, for example ivabradine hydrochloride obtained by the preparation process described in patent specification EP 0 534 859.

The solution may advantageously be seeded during the cooling step.

The acetonitrile or mixture of acetonitrile and water is preferably preheated to a temperature between 60° C. and reflux, more preferably between 65 and 75° C.

The dilution is preferably more than 15 ml/g, more preferably between 50 and 100 ml/g.

The dehydration is preferably performed by heating.

The invention relates also to pharmaceutical compositions comprising as active ingredient the δd-crystalline form of ivabradine hydrochloride together with one or more appropriate, inert and non-toxic excipients. Among the pharmaceutical compositions according to the invention there may be mentioned, more especially, those that are suitable for oral, parenteral (intravenous or subcutaneous) or nasal administration, tablets or dragées, sublingual tablets, capsules, lozenges, suppositories, creams, ointments, dermal gels, injectable preparations and drinkable suspensions.

The useful dosage can be varied according to the nature and severity of the disorder, the administration route and the age and weight of the patient. The dosage varies from 1 to 500 mg per day in one or more administrations.

4

EXAMPLE 2

Pharmaceutical Composition

5 Formula for the preparation of 1000 tablets each containing 5 mg of ivabradine base:

10	Compound of Example 1	5.39 g
	Maize starch	20 g
	Anhydrous colloidal silica	0.2 g
	Mannitol	63.91 g
	PVP	10 g
	Magnesium stearate	0.5 g

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The invention claimed is:

1. A δ -crystalline form of ivabradine hydrochloride of formula (I):

29

25  •HCl.

30 exhibiting essentially the following powder X-ray diffrac-
 tion data, measured using a PANalytical X'Pert Pro diffrac-
 tometer together with an X'Celerator detector and expressed
 in terms of line position (Bragg's angle 2 theta, expressed in
 degrees), line height (expressed in counts), line area (ex-
 35 pressed in counts x degrees), line width at half-height
 ("FWHM", expressed in degrees) and interplanar distance d
 (expressed in Å):

40

	Line no.	Angle 2 theta (degrees)	Height (counts)	Area (counts x degrees)	FWHM (degrees)	Interplanar distance (Å)	
45	1	4.1	414	41	0.1004	21.672	
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	9	16.6	986	163	0.1673	5.345	
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	16	21.4	3112	565	0.184	4.147	
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	23	26.2	1899	313	0.1673	3.397	
	24	26.9	1588	183	0.1171	3.310	
	25	27.6	1357	224	0.1673	3.231	
	26	29.1	140	37	0.2676	3.069	
	65	27	29.5	145	29	0.2007	3.023

65

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	60	21	24.7	256	34	0.1338
22		25.6	309	41	0.1338	3.482
23		26.2	1899	313	0.1673	3.397
24		26.9	1588	183	0.1171	3.310
25		27.6	1357	224	0.1673	3.231
65	26	29.1	140	37	0.2676	3.069
	27	29.5	145	29	0.2007	3.023.

5

2. A process for the preparation of the $\delta\delta$ -crystalline form of ivabradine hydrochloride of claim 1, wherein acetonitrile or a mixture of acetonitrile and water is preheated, ivabradine hydrochloride is added, the solution obtained is allowed to cool at room temperature, held at room temperature until crystallization is complete, and the crystals formed are dehydrated.

3. The process of claim 2, wherein the solution of ivabradine hydrochloride is seeded during the cooling step.

4. A solid pharmaceutical composition comprising as active ingredient the $\delta\delta$ -crystalline form of ivabradine

6

hydrochloride of claim 1, in combination with one or more pharmaceutically acceptable, inert, non-toxic carriers.

5. A method for treating a condition selected from angina pectoris, myocardial infarct and heart failure, such method comprising the step of administering to a living animal body, including a human, a therapeutically effective amount of $\delta\delta$ -crystalline form of ivabradine hydrochloride of claim 1.

* * * * *

2X
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183

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**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES**

Radicación No. 06101550

Clasificación Internacional (IPC): A61K 31/165

Concepto Técnico No. 3559

Patente de Invención

☒

Patente de Modelo de Utilidad

☐

Vía Nacional

☒

Vía PCT (fase nacional)

☐

Cap. I

☐

Cap. II

☐

No. Sol. Internacional

No aplica

Fecha de Presentación Internacional

No aplica

Como resultado del examen definitivo, realizado con fundamento en el artículo 48 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados:

1.1. Descripción: (Folios: 27 a 34).

1.2. Reivindicaciones: 1 a 6 (Folios: 36 a 38).

1.3. Oposiciones: Opositor: Gynopharm S.A. (Folios: 79 a 119).

1.4. Rta. A la Oposición: Folios: 132 a 147.

1.5. Rta del Solicitante: Folios: 167 a 185.

1.6. Prioridad: 11 de octubre de 2005, FR 0510354.

2. Análisis de la Prioridad:

El objeto reivindicado en la presente solicitud corresponde a la prioridad.

3. Objeto de la invención:

La presente solicitud se titula: "Forma cristalina delta d de clorhidrato de ivabradina, su procedimiento de preparación y composiciones farmacéuticas que la contienen".

El objeto de la presente solicitud se refiere a la forma cristalina δ d del clorhidrato de ivabradina de fórmula (I), a su procedimiento de preparación así como a las composiciones farmacéuticas que la contienen.

Según la descripción, la ivabradina, así como sus sales de adición de un ácido farmacéuticamente aceptable, y más particularmente su clorhidrato, tienen propiedades bradicardizantes que hacen que estos compuestos sean útiles en el tratamiento o la prevención de diferentes situaciones clínicas de isquemia miocárdica tales como la angina de pecho, el infarto de miocardio y las alteraciones del ritmo

industrial, y bajo una forma que permitiera una filtración y secado rápidos. Por último, esta forma debería ser perfectamente reproducible, fácilmente formulada y lo suficientemente estable como para permitir su almacenamiento prolongado, sin necesidad de condiciones particulares de temperatura, de luz o de porcentaje de oxígeno.

Reivindicaciones 1 a 1 (folios: 36 y 37): Forma cristalina δ d de clorhidrato de ivabradina de fórmula (I), caracterizada por el diagrama de difracción X sobre polvo, de los folios: 36 y 37.

Reivindicaciones 2 y 3 (folio: 37): Procedimiento de preparación de la forma cristalina δ d del clorhidrato de ivabradina según la reivindicación 1.

Reivindicación 4 (folios: 37 y 38): Composición farmacéutica que contiene como principio activo la forma cristalina δ d del clorhidrato de ivabradina en combinación con uno o varios vehículos inertes, no tóxicos y farmacéuticamente aceptables.

Reivindicaciones 5 y 6 (folio: 38): Utilización de la forma cristalina δ d del clorhidrato de ivabradina según la reivindicación 1, para la fabricación de medicamentos útiles como bradicardizantes (reivindicaciones eliminadas, de acuerdo a la respuesta del solicitante, ver folio: 169).

El problema planteado en esta solicitud es la necesidad de una forma cristalina de la sal clorhidrato de ivabradina, con características interesantes de estabilidad y de procesabilidad.

La solución propuesta por la presente es solicitud consiste en la forma cristalina δ d del clorhidrato de ivabradina.

El objeto de la solicitud definido anteriormente se clasificó en la IPC A61K 31/165.

4. Análisis de la(s) Oposición(es): (artículo 43 D. 486)

Como se dijo en el concepto técnico anterior, la firma opositora Gynopharm S.A. advierte que la presente solicitud carece de Novedad por cuanto el documento ES 2067314 publicado el 16 de marzo de 1995 tiene por objeto (benzo-cicloalquil)-alquilaminas, su procedimiento de preparación y las composiciones farmacéuticas que los contienen, particularmente en la descripción revela compuestos de fórmula (I), particularmente en los ejemplos 1 a 3 se revelan formas cristalinas de (R,S)-7,8-dimetoxi-3-{3-[N-[(4,5-dimetoxi-1-benzo-ciclobutil)-metil]-N-(metil)-amino]-propil}1,3,4,5-tetrahidro-2H-3-benzacepin-2-ona. Como tal se evidencia en estos ejemplos que esta anterioridad divulga también formas cristalinas de clorhidrato de ivabradina (I).

El señor solicitante responde a estas argumentaciones lo siguiente: "... D1 en ninguna parte menciona la preparación y el aislamiento de la forma δ d del hidrocloreto de ivabradine, ni divulga los parámetros de difracción de rayos X..." (Folio: 136).

Con respecto a estos argumentos, se encontró que este documento ES 2067314 efectivamente menciona el clorhidrato de ivabradina y formas cristalinas del mismo, no obstante, no menciona la forma δ d del clorhidrato de ivabradina. Por lo tanto, se reitera que este documento no afecta la Novedad de la presente solicitud, pero sí afecta su Nivel Inventivo, como se verá más adelante en el análisis correspondiente.

5. Determinación del Estado de la Técnica:

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es:

Fecha de presentación de la solicitud prioritaria 11-10-2005.

Teniendo en cuenta la fecha indicada, se buscaron documentos del estado de la técnica relacionados, con fecha de publicación anterior a esta y se encontraron anterioridades que pueden afectar la patentabilidad del objeto de la presente solicitud:

Nº	Documento	Título	Fecha de Publicación
D1	ES 2067314	3-benzacepin-zonas sustituidas por un grupo benzociclobutilo o indanil-alquil-amino-alquilo, útiles en el tratamiento de las afecciones cardiovasculares	16 de marzo de 1995
D2	Libro ¹	Farmacia Remington	1995

6. Análisis de patentabilidad (según requisito) (artículo 14 D486)

6.1. Nivel inventivo (artículo 18 D486)

La presente Solicitud de Patente reivindica lo siguiente: Forma cristalina δ d de clorhidrato de ivabradina de fórmula (I), caracterizada por el diagrama de difracción X sobre polvo, de los folios: 36 y 37.

De igual modo, el procedimiento de preparación de la forma cristalina δ d del clorhidrato de ivabradina según la reivindicación 1 y una composición farmacéutica que contiene como principio activo la forma cristalina δ d del clorhidrato de ivabradina en combinación con uno o varios vehículos inertes, no tóxicos y farmacéuticamente aceptables.

La anterioridad ES 2067314 (folios: 97 a 119) se refiere a 3-benzacepin-zonas sustituidas por un grupo benzociclobutilo o indanil-alquil-amino-alquilo, útiles en el tratamiento de las afecciones cardiovasculares. Entre estos compuestos se encuentra ivabradina así como sus sales farmacéuticamente aceptables entre las que se encuentran las de clorhidrato, por lo tanto, se encuentra el clorhidrato de ivabradina; asimismo, se aprecia en los ejemplos de este documento la obtención de distintas formas cristalinas del clorhidrato de ivabradina, empleando solventes para ello a una temperatura dada y tiempo de cristalización.

El documento "Farmacia de Remington" (folios: 149 a 157) menciona principios básicos de cristales y de polimorfismo, donde también se habla de las técnicas de identificación de estructuras químicas de compuestos aislados entre las cuales están los métodos espectrométricos convencionales (IR, UV, RMN y DRO); una de las técnicas utilizadas es el análisis cristalográfico por rayos X para determinar la estructura tridimensional de una molécula. Allí también se explica que todo compuesto cristalino produce un patrón característico de difracción de rayos X, los cuales pueden ser muy útiles para la identificación y análisis cuantitativo de mezclas sólidas, en la industria farmacéutica para identificar y clasificar formas polimorfas y solvatadas de fármacos.

dosificación. En los últimos años los estudios de rayos X se han acoplado con enfoques gráficos y cuantitativos computarizados de la relación estructura-actividad en un diseño de fármacos asistido por computador (ver folios: 149 a 151, pág. 230 a 235).

En el presente caso, era ya conocida la molécula clorhidrato de ivabradina y, que tras hacer los ensayos de rigor, se encontró que la forma δ del clorhidrato de ivabradina tenía unas propiedades de estabilidad y pureza aceptable para su posterior formulación, así como mejores características para su procesabilidad. Vale la pena decir que en ninguna parte de la solicitud se puede apreciar que en verdad esta forma cristalina tenga ventajas sobre otras formas cristalinas de ivabradina.

También es ampliamente conocido por cualquier persona versada en la materia que para que un compuesto o una sal pueda emplearse como fármaco debe ser estable tanto termodinámicamente como higroscópicamente, de lo contrario no DEBE emplearse a la hora de hacer una formulación para administración a los pacientes. Así pues, se debe realizar una serie de ensayos de preformulación para poder encontrar las formas cristalinas más estables de los compuestos para poderlos incorporar en una forma farmacéutica deseada: tabletas, grageas, cápsulas, jarabes, soluciones, inyectables, etc.

En los estudios de preformulación de cualquier fármaco siempre se evalúa la solubilidad y estabilidad (tanto higroscópica como termodinámica) de dicho principio activo; cuando un fármaco no tiene una velocidad de disolución ni una estabilidad adecuadas, va a haber problemas de biodisponibilidad por lo cual se hace necesario realizar estudios de preformulación que minimicen estos inconvenientes. Las formas más usuales para mejorar condiciones de solubilidad y estabilidad de los fármacos es obteniendo sus sales -en donde los agentes formadores de sal son seleccionados de forma empírica por un químico farmacéutico-, sus cristales -en donde los solventes empleados se seleccionan también en forma empírica-.

Según la Farmacia de Remington (ver página: 2227, folio: 153) la tarea inicial del preformulador consiste en determinar si la sustancia química evaluada existe en más de una forma cristalina. Una vez demostrado que un compuesto existe en más de una forma cristalina se dispone de numerosas técnicas para identificar las distintas fases polimórficas presentes y una de ellas es la difracción de polvo con rayos X.

Cuando se ha determinado que un fármaco existe en más de una forma cristalina es necesario establecer las condiciones en las cuales puede producirse cada una de esas formas. El disolvente de cristalización, la velocidad de cristalización y otros factores pueden determinar que predomine una forma de cristal (ver página: 2229, folio: 154. En cuanto a la formación de sales y selección de los agentes formadores de sal, se tienen en cuenta: la estabilidad química y física, la higroscopicidad, el grado de flujo y la solubilidad (ver página: 2233, folio: 156).

Se reitera que es ampliamente conocido que la cristalización de un polimorfo específico, empieza por la formación de un núcleo, que será el que determina la forma del subsecuente crecimiento cristalino; teóricamente, en una solución supersaturada, se encuentran los núcleos de todos los posibles polimorfos de la sustancia, entonces la cristalización se dará por procesos competitivos; de acuerdo a lo anterior, en condiciones de supersaturación, la primera forma en cristalizar es la termodinámicamente menos estable (la más soluble), esta forma subsecuentemente se disuelve y se transforma en una más estable, el ciclo continúa hasta que solamente el polimorfo termodinámicamente más estable (menos soluble) permanezca.

Siendo que la supersaturación es un factor definitivo en la cristalización polimórfica, igualmente el solvente puede jugar un factor determinante, que no es de naturaleza termodinámica sino cinética.

Es decir, para obtener una forma cristalina se parte de un núcleo que generalmente es el compuesto amorfo o una forma cristalina anterior o un núcleo de la forma cristalina a obtener; se utiliza un solvente de acuerdo con lo que se requiera y un rango de temperatura, que a veces puede ser cercano a la temperatura ambiente, otras veces, temperaturas superiores a los 30 o 40°C. Así pues, el procedimiento de la presente solicitud resulta obvio para una persona versada en la materia y su producto también puesto que es lo que se hace en la práctica normal de investigación de cristales.

El problema técnico planteado en esta solicitud: la necesidad de una forma cristalina de la sal clorhidrato de ivabradina, con características interesantes de estabilidad y de procesabilidad, se había resuelto previamente mediante formas cristalinas de clorhidrato de ivabradina y técnicas de cristalización ya conocidos(as). Por esta razón se considera que la forma cristalina de clorhidrato de ivabradina reivindicadas son evidentes para una persona medianamente versada en la materia.

La(s) reivindicación(es) 1 a 4 de esta solicitud no menciona(n) una característica que conceda un efecto inesperado o especial a ivabradina y su sal clorhidrato, que pueda considerarse como un aporte a la técnica, así que son obvios(as) para una persona versada en la materia.

Además, puesto que D1 y D2 divulgaban previamente formas cristalinas de clorhidrato de ivabradina y técnicas de obtención y de identificación de cristales (folios: 149 a 157), una persona conocedora de la materia motivada por tal sugerencia lograría el objeto de esta solicitud forma cristalina 8d del clorhidrato de ivabradina; de manera que para una persona medianamente versada en la materia sería obvio combinar estos dos documentos. Por lo cual el objeto reivindicado carece de Nivel Inventivo.

7. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento Nº	Reivindicaciones afectadas	Requisito que afecta
D1	ES 2067314	1 a 4	Nivel Inventivo
D2	Farmacia Remington	1 a 4	Nivel Inventivo

8. Respuesta a los argumentos del solicitante:

El señor solicitante afirma lo siguiente: "... Las condiciones halladas por el Solicitante para preparar la forma cristalina de la presente invención no fueron sugeridas por ES 2067314, que no revela la forma cristalina 8d del hidrocloreto de ivabradina ni sugiere que sea posible obtenerla ni la forma en que el individuo capacitado en la técnica puede proceder a fin de obtenerla..." (Folio: 168).

El procedimiento reivindicado en la presente solicitud, que está caracterizado por: "se calienta acetonitrilo o una mezcla de acetonitrilo y agua, se añade el clorhidrato de ivabradina a dicha solución obtenida a temperatura ambiente y se deja..."

impartan nivel inventivo a dicho procedimiento de obtención de cristales. Son las etapas habituales con solventes normalmente empleados y temperatura comúnmente usada.

Tal como enseña el libro "Farmacia Remington", para obtener una forma cristalina se parte de un núcleo que generalmente es el compuesto amorfo o una forma cristalina anterior o un núcleo de la forma cristalina a obtener; se utiliza un solvente de acuerdo con lo que se requiera y un rango de temperatura, que a veces puede ser cercano a la temperatura ambiente, y esto concuerda con lo reclamado en la presente solicitud.

El documento ES 2067314 también divulga procedimientos de obtención de cristales de sales de ivabradina, empleando solventes adecuados y a temperaturas dadas para ello.

Si bien estos documentos no revelan la forma cristalina δ d de clorhidrato de ivabradina, sí sugieren la forma de obtener dicha forma cristalina que es un procedimiento normalmente empleado.

Por lo anterior se puede decir que la formación de cristales δ d de clorhidrato de ivabradina se considera una posibilidad evidente para una persona medianamente versada en la materia enfrentada al problema técnico planteado. No se aprecia Nivel Inventivo, puesto que no hay evidencia de una mejora en la eficacia del compuesto ivabradina que representaría una ventaja inesperada con respecto al arte anterior.

En consecuencia y por todo lo expuesto anteriormente, se recomienda **Negar** el privilegio solicitado para las reivindicaciones: 1 a 4 (folios: 36 a 38).

Bogotá, D.C., 4 de octubre de 2010.

CONCEPTO TÉCNICO No. 3559

EXAMINADOR TÉCNICO
Código No. 202005