



PATENTE DE INVENCION

03-48164

PARENTERAL"

PETITORIO

Industria y Comercio
SUPERINTENDENTE



03 048164 00

SUPERINTENDENCIA Y COMERCIO
NACIONALIDAD: FRANCESA
Fecha (Nº): 2003-06-06 10:00/132
Tramite: 1 VÍA PLI-PNIENT 3/3 FASE NACI 411 PRESENTAL
Dependencia: 2009 DIVISION DE NUEVAS CREACIONES

FORMULARIO UNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

①

SOLICITUD DE:



Patente de Invención



Patente de Modelo de Utilidad



Capítulo I.



Capítulo II.

②

**SOLICITANTE
(71)**

Nombre: **SANOI-SYNTHELABO**

Dirección: 174 avenue de France, F-75013
Paris, Francia

Nacionalidad o Domicilio: Paris, Francia.

Lugar de Constitución: Francia

Teléfono: 3264270 Fax: 6069701

E-mail: jllcco@lloredacamacho.com

IDENTIFICACION

C.C. ☐

NIT ☐

C.E. ☐

Otro ☐

Número _____

③

**REPRESENTANTE
O APODERADO**

Nombre: **JOSE ANTONIO LLOREDA**

Dirección: Calle 72 No. 5-83 Piso 5o.

Teléfono: 3264270 Fax: 6069701

E-mail: jllcco@lloredacamacho.com

C.C. ☒

NIT ☐

C.E. ☐

Otro ☐

Cual _____

Número 17.159.681 TP 10.784

④

**INVENTOR(ES
(72)**

Nombre: **BOURRIAGUE-SEVE, Frédérique y BREUL, Thierry.**

Dirección: Le Village, F-34190 Ferrieres les Verreries y 118, avenue F. de Lesseps, F-34110 Frontignan.

Nacionalidad o Domicilio: FRANCIA

⑤

PCT (86)

Solicitud Internacional No. PCT/FR01/03903

Fecha: 10-12-2001

Publicación Internacional No. WO 02/47880 A1

Fecha: 20-06-2002

⑥

Título (54) "COMPOSICION FARMACEUTICA DE DRONEDARONA PARA ADMINISTRACION PARENTERAL"

⑦

Clasificación Internacional (51) A61K 9/08

⑧

Prioridad

(33) País de Origen

(32) Fecha

(31) Número de Solicitud

SI ☒ NO ☐

FR

11-12-2000

00/16071

⑨

Comprobante de Pago No. 02-86,520 y 03-34,135

Fecha: Diciembre 24, 2002 y Mayo 16, 2003

ANEXOS

10

- ☒ Comprobante de pago de la tasa de presentación de la solicitud.
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Documento de Representación Legal.
- ☒ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones
- ☐ Copia de la solicitud Internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud Internacional al castellano. (Resumen, descripción, reivindicaciones)
- ☒ Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- ☒ Traducción del examen preliminar Internacional efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ 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, relacionados parcial o totalmente con la invención de esta solicitud.
- ☐ De ser el caso, modificaciones efectuadas a la solicitud internacional.
- ☒ Otros: Reporte de Búsqueda Internacional con su traducción, Anexos Reporte de Búsqueda Internacional y Publicación con su traducción.

11

FIGURA CARACTERISTICA:

12

Solicito la concesión de la patente.

NOMBRE:

JOSE ANTONIO LLORERA

FIRMA:

C.C. 17.159.881 Bta. T.P 10.784

RECIBO OFICIAL DE CAJA : 02 - 86,520
FECHA : DICIEMBRE 24 DE 2002



Industria y Comercio

SUPERINTENDENCIA

RECIBO DE CONSIGNACION

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Gr. PAGO
LLORCA Y CIA S. A	CONSIGNACION	BANCO POPULAR	050-00110-6	3139931	24/12/2002	149,623,700.00

RECIBO DE CONCEPTO

CANT.	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	
1	TRAMITES DE SOL. DE PATENTE DE IN	378,000.00
	TOTAL :	\$ 378,000.00

SOL: TRESCIENTOS SETENTA Y OCHO MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Industria y Comercio
Radicación : 0304164 00000000
Fecha (mm): 2002-12-24 10:00/102
Tramite : 011 PLI-PRINCIPI 279 FOLIO 411 PRINCIPAL
Dependencia: 2000 División de Métodos Administrativos

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

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 03 - 34,135
FECHA : MAYO 16 DE 2003

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
LLOREDA Y CIA S. A	CONSIGNACION	BANCO POPULAR	050-00110-6	12125158	16/05/2003	2,830,000.
LLOREDA Y CIA S. A	CONSIGNACION	BANCO POPULAR	050-00110-6	12125159	16/05/2003	2,400.00

***** CONCEPTO *****

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	998 VALOR COMPLEMENTO TARIFA ANO ANTR
		TOTAL : \$ 22,000.00

SOM: VEINTIDOS MIL PESOS

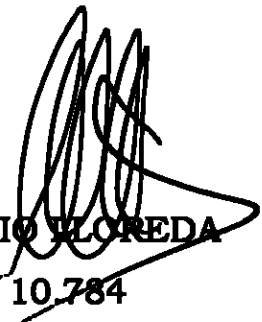
RESPONSABLE : _____

RECEPCIONADO Y CONTROLADO
Radicacion : 030-0164 00000000 Folios: 35
Fecha (MM): 2003-05-06 10:00:00
Tramite : 011 PCI-PALENI 3/9 FINE PALENI 411 PALENI
Dependencia: 2029 DIVISION DE MANEJO ORGANIZACIONES

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

ANEXO

El documento que acredita la calidad de REPRESENTANTES LEGALES en Bogotá de los doctores **JOSE ANTONIO LLOREDA** y/o **GUSTAVO TAMAYO** y/o **ANGELA MARIA RESTREPO** y/o **ALICIA LLOREDA** para TODOS LOS ASUNTOS RELACIONADOS CON LA PROPIEDAD INDUSTRIAL de la sociedad peticionaria, que faculta a cada uno de dichos abogados para actuar individualmente, se esta presentando con esta solicitud. En consecuencia, ruego a usted reconocer la personería de cada uno de dichos Representantes Legales para actuar dentro del presente expediente, a fin de que cualquiera de ellos pueda intervenir en cualquier tiempo respecto de la solicitud en él contenida.



JOSE ANTONIO LLOREDA

T.P. No. 10.784

Código 231

TRADUCCION OFICIAL No 705

TRADUCCION DE UN DOCUMENTO PRESENTADO EN INGLES. PODER DE REPRESENTACION LEGAL OTORGADO A JOSE ANTONIO LLORED A Y/O GUSTAVO TAMAYO Y/O ANGELA MARIA RESTREPO Y/O ALICIA LLORED A Y/O JOSE LLORED A CAMACHO por SANOFI-SYNTHELABO.

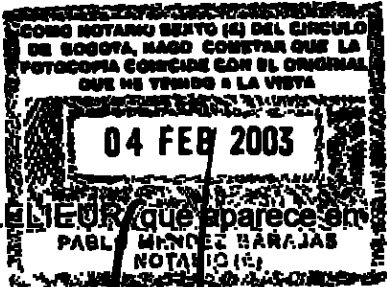
PODER

Dado y firmado el 14 de Agosto, 2001

Firmado: **Christophe LELIEUR – Abogado de Marcas**

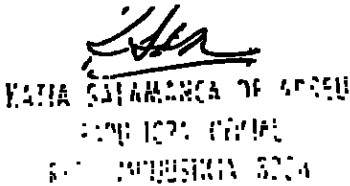
EL NOTARIO DEBE FIRMAR AL RESPALDO

Visto para certificación de la firma del Sr. Christophe LELIEUR que aparece en documento adjunto



Firmado: (firma ilegible)

Sello en altorrelieve del Notario de París Alain Koenig



SANOFI-SYNTHELABO

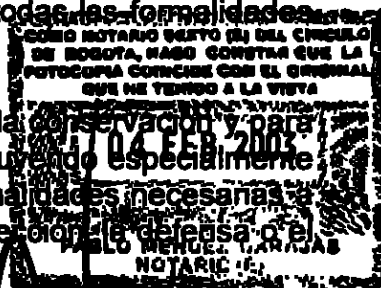
Sociedad Anónima con un capital de 1 462 286 436 Euros
Sede social: 174, avenue de France 75013 PARIS
395 030 844 R.C.S. PARIS

SUBDELEGACION DE PODERES

El Director Jurídico, debidamente facultado para tal efecto por medio del presente por delegación de poderes, a 19 de Mayo de 1999 del Señor Jean-Francois DEHECQ, Presidente de la Junta Directiva de la sociedad SANOFI-SYNTHELABO,

Subdelega a Christophe LELIEUR, Jurista del Departamento de "Marcas", empleado del SANOFI-SYNTHELABO GROUPE, sociedad anónima con un capital de 26 216 576 Euros, con sede social en 174, avenue de France 75013 PARIS – Francia – habiendo precisado que la sociedad SANOFI-SYNTHELABO GROUPE es propiedad 100% de la sociedad SANOFI-SYNTHELABO, a fin de que haga uso de ellos en nombre y por cuenta de la sociedad SANOFI-SYNTHELABO, los poderes de:

- Requerir del Instituto Nacional de la Propiedad Industrial, o de toda oficina extranjera nacional o supranacional, el depósito y el registro de toda marca, todo modelo, diseño, sigla, logotipo, y de llevar a cabo todas las formalidades necesarias a efecto de obtener su registro;
- Firmar todo documento necesario para el depósito, para la conservación y para todo procedimiento relativo a las marcas y modelos, incluyendo especialmente el procedimiento de oposición, y efectuar todas las formalidades necesarias a efecto de asegurar el mantenimiento en vigencia, la protección, la defensa o el retiro de dichas marcas y modelos.



Y, en consecuencia, presentar todas las solicitudes, firmar y aprobar todas los documentos, pagar todos los impuestos, retirar todos los títulos, sustituir los poderes total o parcialmente, y hacer en general todo lo que sea útil para la ejecución de la presente delegación.

APOSTILLA

(Convención de La Haya del 5 de Octubre 1961)

1. República Francesa

El presente acto público

2. ha sido firmado por el Sr. KOENIG

3. actuando en su condición de NOTARIO

4. lleva el sello del SU OFICINA

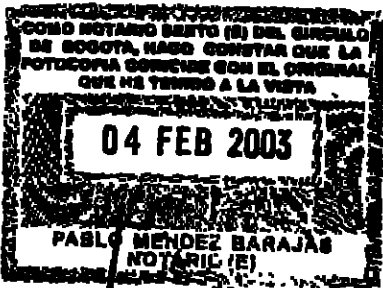
CERTIFICADO

5. En París, el 23 de Agosto, 2001

7. Por el Procurador General de la Corte de Apelación

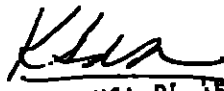
8. Bajo el No. **55792 /01**

9. Sello de la Corte de Apelación de París.



Firma

Firmado: (firma ilegible)


KATIA SALAMANCA DE ARREU
TRADUCTORA OFICIAL
RES. MINJUSTICIA 3288

MINISTERIO DE RELACIONES
EXTERIORES

182830
Katia Soho
IVATIRMA APARECE EN EL
JORNAL DE BOGOTÁ
AS 11:31

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

2001 OCT 23 A 11: 31
A. V.
JEFE DE LEGALIZACIONES
SECRETARÍA DE BOGOTÁ D.C.

**SECRETARIA DEL TRIBUNAL DE COMERCIO DE PARIS
1 QUAI DE CORSE
75181 PARIS CEDEX 04**

REFERENCIA 0100099801 / MINITEL

EXTRACTO DEL REGISTRO COPORATIVO

EXTRACTO K^{BIS}

MATRICULA EN EL REGISTRO CORPORATIVO

EN LA FECHA: MAYO 18 1994

NUMERO DE REGISTRO DE COMERCIO:

R.C.S. PARIS B 395 030 844 (1999B00375)

EXTRACTO DE: Julio 19, 2001

INFORMACIONES RELATIVAS A LA ENTIDAD CORPORATIVA

RAZON SOCIAL

SANOFI-SYNTHELABO

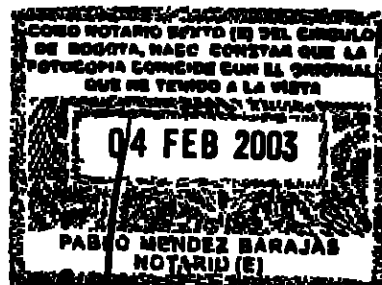
FORMA JURIDICA: SOCIEDAD ANONIMA

CON UN CAPITAL DE: 1,462,883,492 EUROS

DIRECCION DE LA SEDE PRINCIPAL

1 74 AVENUE DE FRANCE

75013 PARIS, FRANCIA



Katia Salazar
KATIA SALAZAR
TRADUCTORA OFICIAL
RES. MINISTRIA 3298

DURACION DE LA SOCIEDAD: HASTA MAYO 18, 2093
FECHA DE CIERRE DE CUENTAS EL 31 DE DICIEMBRE

CONSTITUCION:

PRESENTACION DEL ACTA: MAYO 17 1994, No. 011745, ANTE EL
REGRISTRADOR DEL TRIBUNAL COMERCIAL DE NANTERRE
PUBLICACION LEGAL: MAYO 12, 1994, LA GAZETTE DU PALAIS

TRANSFERIDO DE NANTERRE

PRESENTACION DEL ACTA EN LA SECRETARIA DE PARIS EL 11 DE ENERO
1999 NUMERO 000450
PUBLICACION LEGAL DE LA NUEVA SEDE: DICIEMBRE 24, 1998 LE
PUBLICATERUR LEGAL.

ADMINISTRACION

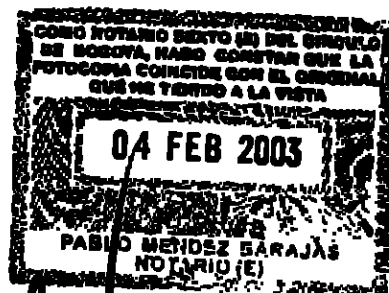
PRESIDENTE DE LA JUNTA DIRECTIVA

SR. DEHECQ, JEAN-FRANCOIS

FECHA NACIMIENTO: ENERO 1, 1940
LUGAR DE NACIMIENTO: 44000 NANTES
PAIS: FRANCIA
NACIONALIDAD: FRANCESA
DIRECCION: 28, RUE ADRIEN-MOISANT
78400 CHATOU, FRANCIA

DIRECTOR

DIRECCION: L'OREAL
14, RUE ROYALE



KATIA SALAMANCA DE
TRADUCTORA OFICIAL
RES. MINJUSTICIA 5268

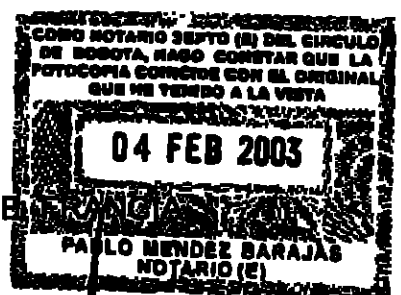
75008 PARIS, FRANCIA

REGISTRO CORPORATIVO DE PARIS No:

R.C.S B632012100
REPRESENTADO POR: SR. SOMNOTET, MICHEL PIERRE RAOUL
FECHA NACIMIENTO: FEBRERO 6, 1940
LUGAR NACIMIENTO: 37110 CHÂTEAU RENAULT
PAIS: FRANCIA
NACIONALIDAD: FRANCESA
DIRECCIÓN: 52 AVENUE BOSQUET
75007 PARIS, FRANCIA

FUNCIONARIO EJECUTIVO JEFE & DIRECTOR

SR. GUÉRIN, HERVÉ BERNARD LUCIEN
FECHA NACIMIENTO: JULIO 4, 1941
LUGAR NACIMIENTO: RABAT
PAIS: MARRUECOS
NACIONALIDAD: FRANCESA
DIRECCIÓN: 17, AVENUE DE MADRID
92200 NEULLY-SUR-SEINE



DIRECTOR: SR. BARBIER DE LA SERRE, RENE PAUL
FECHA NACIMIENTO: JULIO 3, 1940
LUGAR NACIMIENTO: 22770 LANCIEUX
PAIS: FRANCIA
NACIONALIDAD: FRANCESA
DIRECCIÓN: 26, RUE BARBET-DE-JOUY

Katia Salama
KATIA SALAMA
TRADUCTORA OFICIAL
RES. MINISTRIA 3268

75007 PARIS, FRANCIA

DIRECTOR: SR. CASTRES SAINT-MARTIN, PIERRE HENRI
JOSEPH GUY

FECHA NACIMIENTO: ABRIL 12, 1936

LUGAR NACIMIENTO: 92100 BOULOGNE-BILLANCOURT

PAIS: FRANCIA

NACIONALIDAD: FRANCESA

DIRECCIÓN: 11, RUE DE PORTO-RICHE
92190 MEUDON, FRANCIA

DIRECTOR: ELF AQUITAINE S.A.

DIRECCIÓN: TOUR ELF
2, PLACE DE LA COUPOLE
LA DEFENSE 6
92400 COURBEVOIE, FRANCIA

REGISTRO CORPORATIVO DE NANTERRE No.:

R.C.S. B 552120784

REPRESENTADO POR:

SR. LEON, JEAN-PAUL EMMANUEL

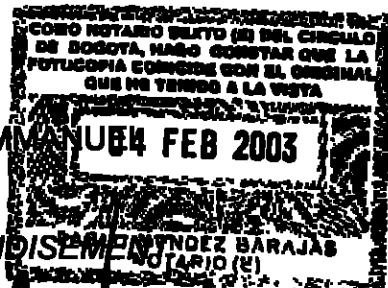
FECHA DE NACIMIENTO: JULIO 27, 1937

LUGAR NACIMIENTO: 75016 PARIS 16TH ARRONDISSEMENT

PAIS: FRANCIA

NACIONALIDAD: FRANCESA

DIRECCIÓN: 10^{BIS}, AVENUE DES GOBELINS
75005 PARIS, FRANCIA

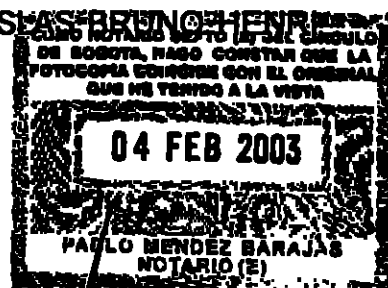


Katia
KATIA SALAMANCA DE ABREU
TRADUCTORA
RES. INMUTABILIDAD 3248

DIRECTOR: SR. DE GENNES, PIERRE GILLES ROBERT
YVES
FECHA DE NACIMIENTO: OCTUBRE 24, 1932
LUGAR NACIMIENTO: 75016 PARIS 16TH ARRONDISSEMENT
PAIS: FRANCIA
NACIONALIDAD: FRANCESA
DIRECCIÓN: 10, RUE VAUQUELIN
75005 PARIS, FRANCIA

DIRECTOR: SR. OWEN JONES, LINDSAY HARWOOD
FECHA DE NACIMIENTO: MARZO 17, 1946
LUGAR NACIMIENTO: WALLASEY
PAIS: REINO UNIDO
NACIONALIDAD: BRITANICA
DIRECCIÓN: 14, RUE ROYALE
75005 PARIS, FRANCIA

DIRECTOR: SR. WEYMULLER, STANISLAS-BENOIT-HERNANDEZ
ERNEST
FECHA DE NACIMIENTO: SEPTIEMBRE 5, 1948
LUGAR NACIMIENTO: 68100 MULHOUSE
PAIS: FRANCIA
NACIONALIDAD: FRANCESA
DIRECCIÓN: 12, RUE PAUL-VALERY
75005 PARIS, FRANCIA



DIRECTOR: SR. CASTAIGNE, ROBERT MARIE PAUL
FECHA DE NACIMIENTO: ABRIL 27, 1946

Katia
KATIA SAPAMANCA DE CASTAIGNE
12/05/2004
RES. NOTARIAL 3268

LUGAR NACIMIENTO: 52100 ST DIZIER
 PAIS: FRANCIA
 NACIONALIDAD: FRANCESA
 DIRECCIÓN: 8, AVENUE CHARLES DE GAULLE
 92100 BOULOGNE BILLANCOURT

DIRECTOR: SR. DESMAREST THIERRY
 FECHA DE NACIMIENTO: DICIEMBRE 18, 1945
 LUGAR NACIMIENTO: 75012 PARIS, 12TH ARRONDISSEMENT
 PAIS: FRANCIA
 NACIONALIDAD: FRANCESA
 DIRECCIÓN: 189 BOULEVARD SAINT GERMAIN
 75007 PARIS, FRANCIA

AUDITOR LEGAL TITULAR

ERNST & YOUNG AUDIT S.A.

DIRECCION: 4 RUE AUBER
 75009 PARIS, FRANCIA

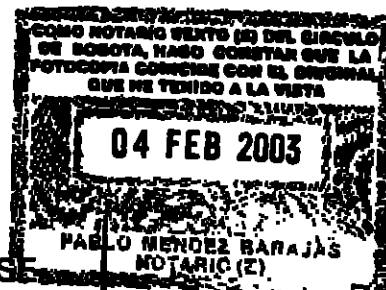
REGISTRO CORPORATIVO DE PARIS No.:
 R.C.S. B344366315

AUDITOR LEGAL TITULAR

BEFEC-PRICE WATERHOUSE

DIRECCIÓN: 11, RUE MARGUERITTE
 75017 PARIS, FRANCIA

REGISTRO CORPORATIVO DE PARIS No.:
 R.C.S. B672006483



Katia
 KATIA SALAMANCA DE ADRU
 TRADUCTORA OFICIAL
 RES. MINJUSTICIA 3268

AUDITOR LEGAL SUPLENTE:

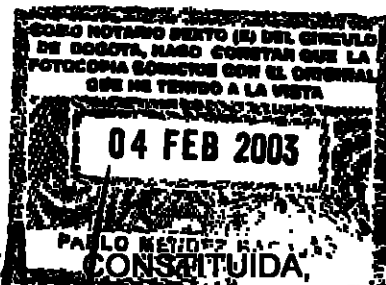
SR. PERRIN, BRUNO
FECHA NACIMIENTO: DICIEMBRE 3, 1955
LUGAR NACIMIENTO: NUEVA YORK
PAIS: ESTADOS UNIDOS DE AMERICA
NACIONALIDAD: FRANCESA
DIRECCION: 100, RUE RAYMOND-LOSSERAND
75014 PARIS, FRANCIA

AUDITOR LEGAL SUPLENTE:

SR. DENIZEAU, JACQUES
FECHA NACIMIENTO: OCTUBRE 23, 1949
LUGAR NACIMIENTO: 49 ANGERS
PAIS: FRANCIA
NACIONALIDAD: FRANCESA
DIRECCION: 11, RUE MARGUERITTE
75017 PARIS, FRANCIA

INFORMACION RELATIVA A LA ACTIVIDAD COMERCIAL:

ORIGEN DE LA COMPAÑIA: ESTA COMPAÑIA, YA CONSTITUIDA,
TRANFIERE SU SEDE PRINCIPAL DE 2,
PLACE DE LA COUPOLE, 92400
COURBEVOIE, FRANCIA
A PARTIR DE DICIEMBRE 18, 1998, No. DE
REGISTRO CORPORATIVO ANTERIOR
94B02598



Katia Salamanca de Abreu
KATIA SALAMANCA DE ABREU
INSTRUCTORA OFICIAL
RES. MINJUSTICIA 3288

ORIGEN DEL NEGOCIO: ESTABLECIMIENTO

ACTIVIDAD CORPORATIVA: TOMA DE INTERESES Y DE PARTICIPACIONES EN TODAS LAS EMPRESAS O SOCIEDADES ESPECIALMENTE EN LOS SECTORES DE LA SALUD Y DE LA QUIMICA FINA, DE LA TERAPEUTICA HUMANA Y ANIMAL, DE LA NUTRICION Y DE LAS BIOINDUSTRIAS.

DIRECCION DEL ESTABLECIMIENTO PRINCIPAL

174, AVENUE DE FRANCE
75013 PARIS, FRANCIA

COMIENZO DE LA OPERACION MAYO 11, 1994

MODO DE OPERACION DIRECTA

OBSERVACIONES

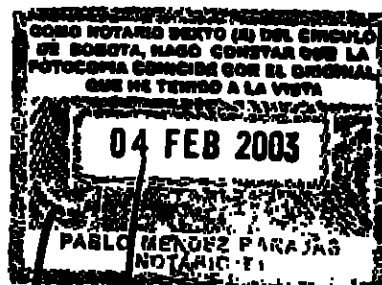
FECHA: 11 DE ENERO 1999

OBSERVACION No. 81033

LA COMPAÑIA NO MANTIENE NINGUNA ACTIVIDAD EN LA ANTIGUA SEDE PRINCIPAL

FECHA: 16 DE JUNIO 1999

OBSERVACION No. 16154



Katia Salamanca de Arreola
KATIA SALAMANCA DE ARREOLA
INSTRUMENTO OFICIAL
RES. 14000/1999 3288

COMPAÑÍA QUE PARTICIPO EN LA FUSION:

NOMBRE CORPORATIVO: SANOFI
ESTRUCTURA LEGAL: SOCIEDAD ANOMINA
SEDE PRINCIPAL: 174, AVENUE DE FRANCE
75013 PARIS, FRANCIA
REGISTRO CORPORATIVO DE PARIS No.:
R.C.S. 732 059 332

FECHA: JUNIO 29, 1999
OBSERVACION No. 18854

COMPAÑÍA QUE PARTICIPO EN LA FUSION:

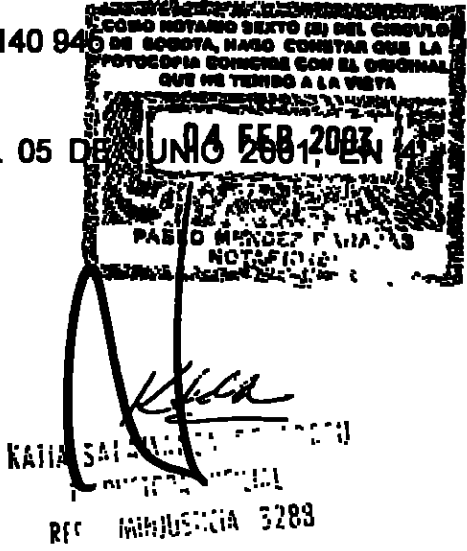
NOMBRE CORPORATIVO: SYNTHELABO
ESTRUCTURA LEGAL: SOCIEDAD ANOMINA
SEDE PRINCIPAL: 22, AVENUE GALILEE
92350 LE PLESSIS-ROBINSON,
FRANCIA
REGISTRO CORPORATIVO DE NANTERRE No.:
R.C.S. B572 140 946

EXTRACTO EXPEDIDO EN PARIS, FRANCIA EL 05 DE JUNIO 1999
PAGINAS.

EL REGISTRADOR,

Firma (en blanco)

DERECHOS DE REGISTRO DEL TRIBUNAL



(Decreto 86.1098 de Octubre 10, 1986)

antes de impuestos: 0.00 FRF

EXTRACTO DE REGISTRO CORPORATIVO

EXTRACTO DE MAYO 31, 2001

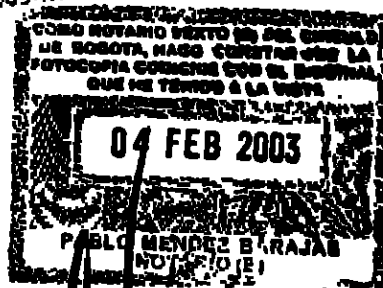
0.00% V.A.T.: 0.00 FRF

I.E. Total excluidos impuestos: 0.00 FRF

TODA COPIA DEL PRESENTE DOCUMENTO, AUN CERTIFICADA COMO
AUTENTICA Y PRECISA, NO TIENE VALIDEZ

===== FIN DEL EXTRACTO =====


KATIA SALAMANCA DE ADREU
TRABAJADORA OFICIAL
RES. MINUSUCIA 3288

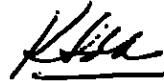


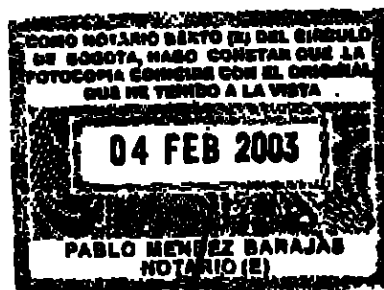
SECRETARIA DEL TRIBUNAL DE COMERCIO DE PARIS
1 QUAI DE CORSE
75181 PARIS CEDEX 04

REFERENCIA 0100099601 / MINITEL

EXTRACTO DEL REGISTRO COPORATIVO
EXTRACTO K^{BIS}

MATRICULA EN EL REGISTRO CORPORATIVO


KATIA SALAMANCA DE ARREU
TRADUCTORA OFICIAL
RES. MINJUSHCIA 3288



APOSTILLA

(Convención de La Haya del 5 de Octubre 1961)

1. República Francesa

El presente acto público

2. ha sido firmado por (nombre ilegible)

3. actuando en su condición de (ilegible)

4. lleva el sello de (ilegible)

CERTIFICADO

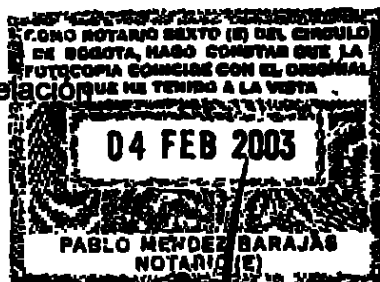
MINISTERIO DE RELACIONES
EXTERIORES
182831
KATIA SALAMANCA
HATFIMA ARAPECE EL
NOTARIO DESDE
AS FIRMES TRIN

5. En París, el 9/10/01

7. Por el Procurador General de la Corte de Apelación

8. Bajo el No. 69147

9. Sello de la Corte de Apelación de París.



NO SE ASUME
RESPONSABILIDAD DEL TEXTO
2001 OCT 23 A 11:31
JEF DE LEGALIZACIONES
SALAME DE BOGOTA D.C.

Firma
Firmado: (firma ilegible)

KATIA SALAMANCA DE ABREU
OFICIAL
R.F. JUSTICIA 2228

abajo firmados.

SANOFI-SYNTHELABO, una sociedad organizada y existente de conformidad con las leyes de Francia,

con domicilio en

174 avenue de France, 75013 Paris, France

nombramos por el presente a JOSE ANTONIO LLOREDA, y/o GUSTAVO TAMAYO, y/o ANGELA MARIA RESTREPO, y/o ALICIA LLOREDA, y/o JOSE LLOREDA CAMACHO, domiciliados en Bogotá, Colombia, con oficinas en dicha ciudad, Calle 72 No. 5-83, piso 6^{ta}, nuestros representantes legales y verdaderos en Bogotá, con facultades para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales, con el fin de dar cumplimiento al parágrafo lo. del artículo 543 del decreto 410 de 1971.

Los doctores JOSE ANTONIO LLOREDA, y/o GUSTAVO TAMAYO, y/o ANGELA MARIA RESTREPO, y/o ALICIA LLOREDA, y/o JOSE LLOREDA CAMACHO, o los apoderados que cualquiera de ellos designe, quedan especialmente facultados para representarnos ante las autoridades colombianas, administrativas, judiciales o de policía, en todos los trámites relativos a la propiedad industrial, a cuyo efecto les facultamos para dar ante dichas autoridades todos los pasos necesarios al objeto indicado; elevar solicitudes, declaraciones y reclamos; formular descripciones, enmiendas, oposiciones y apelaciones; instaurar cancelaciones y amparos administrativos; abonar todos los impuestos y cuotas y efectuar todo otro pago determinado por la ley; recibir todos los documentos y valores, dando el descargo respectivo; llenar cualesquiera otros requisitos y tomar, en fin, todas las medidas que creyeren conducentes al resguardo de nuestros intereses; y en caso de producirse oposición, pasando los antecedentes a los tribunales, quedan facultados para tomar intervención como demandantes o demandados ante los jueces que sean competentes, pudiendo transar, someter a árbitros, desistir, percibir y apelar, con todas las demás facultades que resulten necesarias, y por el presente declaramos desde ahora válido y bueno cuanto dichos representantes y/o los apoderados que cualquiera de ellos nombre hicieren en nuestro beneficio.

Asimismo, facultamos a los doctores JOSE ANTONIO LLOREDA, y/o GUSTAVO TAMAYO, y/o ANGELA MARIA RESTREPO, y/o ALICIA LLOREDA, y/o JOSE LLOREDA CAMACHO, para solicitar en la Oficina de Propiedad Industrial la protocolización de este documento y de cualquier poder que cualquiera de ellos otorgue a nombre nuestro, así como para sustituir el presente.

Dado y firmado el 14 de Agosto de 2001

Vu pour certification
matérielle de la signature
de M. Christophe LELIEUR
apposée ci -

The undersigned,

SANOFI-SYNTHELABO, a corporation organized and existing under the laws of France,

of

174 avenue de France, 75013 Paris, France.

hereby appoint JOSE ANTONIO LLOREDA, and/or GUSTAVO TAMAYO, and/or ANGELA MARIA RESTREPO, and/or ALICIA LLOREDA, and/or JOSE LLOREDA CAMACHO, of Bogota, Colombia, with offices in said town, Calle 72 No. 5-83, Sixth Floor, our true and legal representatives in Bogotá, with power to receive notifications and to appoint judicial or extrajudicial agents, so as to comply with paragraph 1 of article, 543 of decree 410 of 1971.

Doctors JOSE ANTONIO LLOREDA, and/or GUSTAVO TAMAYO, and/or ANGELA MARIA RESTREPO, and/or ALICIA LLOREDA, and/or JOSE LLOREDA CAMACHO, or the agents by any one of them appointed, are especially empowered to represent us before the administrative, judicial or police authorities of Colombia, in all proceedings pertaining to industrial property, for which purpose we authorize them to take before the said authorities all the necessary steps to the said end; to file petitions, declarations, claims, cancellations and administrative Injunction proceedings; to draw up specifications; to make amendments, oppositions and appeals, to pay all installments and effect all other payments prescribed by law; to receive proper receipts, to comply with all other requirements and, in short, to take all those measures which they may deem fit for the protection of our interests, and in cast, of opposition, where the proceedings be passed over to the courts, we authorize said agents to act on our behalf, as competent legal representatives, before the competent authorities, with power to make arrangements, to transact, to desist, to collect, to appeal and, in short, with all such further powers as may be required, and we hereby declare from now on valid and good all that said representatives and/or agents by any one of them appointed may do.

We also authorize doctors JOSE ANTONIO LLOREDA, and/or GUSTAVO TAMAYO, and/or ANGELA MARIA RESTREPO, and/or ALICIA LLOREDA, and/or JOSE LLOREDA CAMACHO, to apply for protocolization of this document and of any power of attorney by any one of them conferred in our name, before the Office of Industrial Property, as well as to substitute these presents.

Given and signed this Tuesday August 14th, 2001


Christophe LELIEUR - Trademark Lawyer

NOTARY SHOULD EXECUTE OTHER SIDE



Signature

Sous No

7. - Par le Procureur Général près la Cour d'Appel

5. - à Paris le 23 AOÛT 2001

ATTESTE

4. - est revêtu du sceau de

3. - agissant en qualité de

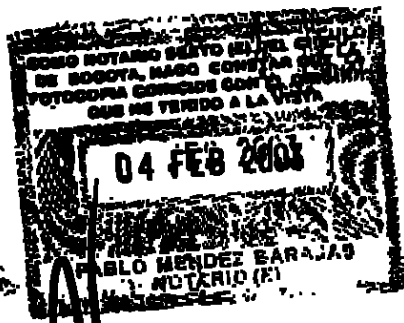
2. - a été signé par

Le présent acte public

1. - République Française

(Convention de La Haye du 5 Octobre 1961)

APOSTILLE



SANOFI-SYNTHELABO

Société Anonyme au capital de 1 462 286 436 €
Siège social : 174, avenue de France 75013 PARIS
395 030 844 R.C.S. PARIS

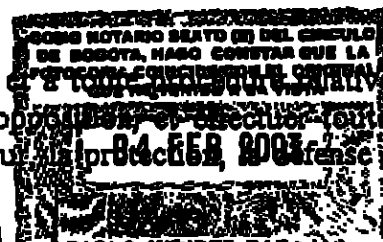
SUBDELEGATION DE POUVOIRS

Directeur Juridique, dûment habilité à l'effet des présentes par délégation de pouvoirs en date du 19 mai 1999 de Monsieur Jean-François DEHECQ, Président du conseil d'administration de la société SANOFI-SYNTHELABO,

subdélègue à Christophe LELIEUR, Juriste au Département « Marques », salarié de la SANOFI-SYNTHELABO GROUPE, société anonyme au capital de 26 216 576 Euros, ayant son siège social 174, avenue de France 75013 PARIS - France - étant précisé que la société SANOFI-SYNTHELABO GROUPE est détenue à 100 % par la société SANOFI-SYNTHELABO, afin qu'il en fasse usage au nom et pour le compte de la société SANOFI-SYNTHELABO, les pouvoirs de :

- requérir de l'Institut National de la Propriété Industrielle, ou de tout office ou bureau étranger national ou supranational, le dépôt et l'enregistrement de toute marque, tout modèle, dessin, sigle, logotype, et effectuer toutes les formalités nécessaires à l'effet d'obtenir leur enregistrement ;
- signer tout document nécessaire au dépôt, à la conservation et à toute procédure relative aux marques et modèles, y compris notamment la procédure d'opposition, et effectuer toutes les formalités nécessaires à l'effet d'assurer le maintien en vigueur de la protection, la défense ou le retrait desdits marques et modèles.

Et, en conséquence, présenter toutes requêtes, signer et approuver toutes pièces, verser toutes taxes, retirer tous titres, substituer tout ou partie des présents pouvoirs, faire généralement tout ce qui est utile pour l'exécution de la présente délégation.



E X T R A I T K B I S

IMMATRICULATION AU REGISTRE DU COMMERCE ET DES SOCIETES
EN DATE DU : 18 MAI 1994
NUMERO DE REGISTRE DU COMMERCE :
R.C.S. PARIS B 395 030 844 (1999B00375)
EXTRAIT AU : 09 SEPTEMBRE 2001

RENSEIGNEMENTS RELATIFS A LA PERSONNE

RAISON SOCIALE (DENOMINATION) - SIGLE
SANOFI-SYNTHELABO

FORME JURIDIQUE : SOCIETE ANONYME
AU CAPITAL DE 1.462.883.492 EUR

ADRESSE DU SIEGE
174 AVE DE FRANCE 75013 PARIS

DUREE DE LA SOCIETE : JUSQU'AU 18 MAI 2093
DATE D'ARRETE DES COMPTES LE 31 DECEMBRE

CONSTITUTION
DEPOT DE L'ACTE : LE 17 MAI 1994 NUMERO 011745 AU GREFFE DU
TRIBUNAL DE NANTERRE
PUBLICATION : JOURNAL LA GAZETTE DU PALAIS DU 12 MAI 1994

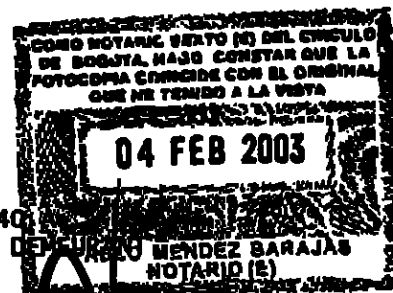
TRANSFERT DE NANTERRE

DEPOT D'ACTE AU GREFFE DE PARIS LE 11 JANVIER 1999 NUMERO 000450
PUBLICATION AU GREFFE DU NOUVEAU SIEGE : JOURNAL LE PUBLICATEUR
LEGAL DU 24 DECEMBRE 1998

ADMINISTRATION

PRESIDENT DU CONSEIL D'ADMINISTRATION MONSIEUR DEHECQ JEAN-FRANCOIS
NE(E) LE 01 JANVIER 1940 COMMUNE DE NAISSANCE NANTES 44000 PAYS
FRANCE
NATIONALITE FRANCAISE
28 R ADRIEN MOISANT 78400 CHATOU

ADMINISTRATEUR L'OREAL
14 R ROYALE 75008 PARIS
NO RCS PARIS B632012100
REPRESENTEE PAR
MONSIEUR SOMNOLET MICHEL PIERRE RAOUL NE(E) LE 06 02 1940
CHATEAU RENAULT 37110 PAYS FRANCE NATIONALITE FRANCAISE
52 AV BOSQUET 75007 PARIS



PAGE 01

Le mot "ORIGINAL" ci-dessus signifie que vous êtes en présence d'un original émanant du greffe

EXTRAIT K B I S

EXTRAIT AU 09 SEPTEMBRE 2001

ADMINISTRATEUR MONSIEUR GUERIN HERVE BERNARD LUCIEN
NE(E) LE 04 JUILLET 1941 COMMUNE DE NAISSANCE RABAT PAYS MAROC
NATIONALITE FRANCAISE
17 AV DE MADRID 92200 NEUILLY SUR SEINE

ADMINISTRATEUR MONSIEUR BARBIER DE LA SERRE RENE PAUL
NE(E) LE 03 JUILLET 1940 COMMUNE DE NAISSANCE LANCIEUX 22770 PAYS
FRANCE
NATIONALITE FRANCAISE
26 R BARBET DE JOUY 75007 PARIS

ADMINISTRATEUR MONSIEUR CASTRES SAINT MARTIN PIERRE HENRI JOSEPH GUY
NE(E) LE 12 AVRIL 1936 COMMUNE DE NAISSANCE BOULOGNE BILLANCOURT
92100 PAYS FRANCE
NATIONALITE FRANCAISE
11 R DE PORTO RICHE 92190 MEUDON

ADMINISTRATEUR ELF AQUITAINE - SA
TOUR ELF - 2 PCE DE LA COUPOLE LA DEFENSE 6 92400 COURBEVOIE
NO RCS NANTERRE B552120784
REPRESENTEE PAR
MONSIEUR LEON JEAN PAUL EMMANUEL NE(E) LE 27 07 1937 A PARIS 75016
ARRONDISSEMENT 16 PAYS FRANCE NATIONALITE FRANCAISE DEMEURANT 10
BIS AVENUE DES GOBELINS 75005 PARIS

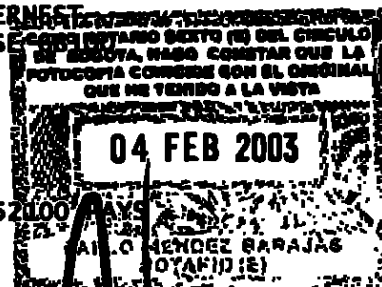
ADMINISTRATEUR MONSIEUR DE GENNES PIERRE GILLES ROBERT YVES
NE(E) LE 24 OCTOBRE 1932 COMMUNE DE NAISSANCE PARIS 75016
ARRONDISSEMENT 16 PAYS FRANCE
NATIONALITE FRANCAISE
10 R VAUQUELIN 75005 PARIS

ADMINISTRATEUR MONSIEUR OWEN JONES LINDSAY HARWOOD
NE(E) LE 17 MARS 1946 COMMUNE DE NAISSANCE WALLASEY PAYS
ROYAUME-UNI
NATIONALITE ROYAUME UNI
14 R ROYALE 75008 PARIS

ADMINISTRATEUR MONSIEUR WEYMULLER STANISLAS BRUNO HENRI ERNEST
NE(E) LE 05 SEPTEMBRE 1948 COMMUNE DE NAISSANCE MULHOUSE
PAYS FRANCE
NATIONALITE FRANCAISE
2 PCE DE LA COUPOLE 92400 COURBEVOIE

ADMINISTRATEUR MONSIEUR CASTAIGNE ROBERT MARIE PAUL
NE(E) LE 27 AVRIL 1946 COMMUNE DE NAISSANCE ST DIZIER 52000 PAYS
FRANCE
NATIONALITE FRANCAISE
2 PCE DE LA COUPOLE 92400 COURBEVOIE

ADMINISTRATEUR MONSIEUR DESMAREST THIERRY
NE(E) LE 18 DECEMBRE 1945 COMMUNE DE NAISSANCE PARIS 75012
ARRONDISSEMENT 12 PAYS FRANCE



PAGE 02

Le mot "ORIGINAL" ci-dessus signifie que vous êtes en présence d'un original émanant du greffe

E X T R A I T K B I S

EXTRAIT AU 09 SEPTEMBRE 2001

NATIONALITE FRANCAISE
2 PL DE LA COUPOLE 92400 COURBEVOIE

COMMISSAIRE AUX COMPTES TITULAIRE ERNST & YOUNG AUDIT
4 R AUBER 75009 PARIS
NO RCS PARIS B344366315

COMMISSAIRE AUX COMPTES TITULAIRE BEFEC - PRICE WATERHOUSE
11 RUE MARGUERITTE 75017 PARIS
NO RCS PARIS B672006483

COMMISSAIRE AUX COMPTES SUPPLEANT MONSIEUR PERRIN BRUNO
NE(E) LE 03 DECEMBRE 1955 COMMUNE DE NAISSANCE NEW YORK PAYS
ETATS-UNIS D'AMERIQUE
NATIONALITE FRANCAISE
100 R RAYMOND LOSSERAND 75014 PARIS

COMMISSAIRE AUX COMPTES SUPPLEANT MONSIEUR COLL PIERRE
NE(E) LE 15 DECEMBRE 1954 COMMUNE DE NAISSANCE OUAGADOUGOU PAYS
BURKINA FASO
NATIONALITE FRANCAISE
11 R MARGUERITTE 75017 PARIS

RENSEIGNEMENTS RELATIFS A L'ACTIVITE COMMERCIALE :

ORIGINE DE LA SOCIETE : CETTE SOCIETE ,DEJA CONSTITUEE, TRANSFERE
SON SIEGE DE 2 PL DE LA COUPOLE 92400 COURBEVOIE
A COMPTER DU 18 DECEMBRE 1998 ANCIEN N° RCS.94802598

ORIGINE DU FONDS : CREATION D'UN FONDS DE COMMERCE

ACTIVITE : ACTIVITE DE PRISES D'INTERETS ET DE PARTICIPATIONS DANS
TOUTES ENTREPRISES OU SOCIETES NOTAMMENT DES SECTEURS DE LA SANTE
ET DE LA CHIMIE FINE, DE LA THERAPEUTIQUE HUMAINE ET ANIMALE, DE
LA NUTRITION ET DES BIOS INDUSTRIES

ADRESSE DU PRINCIPAL ETABLISSEMENT
174 AVE DE FRANCE 75013 PARIS

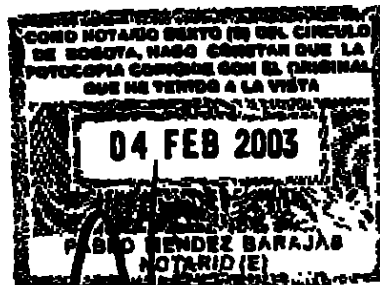
DEBUT D'EXPLOITATION LE 11 MAI 1994

MODE D'EXPLOITATION : EXPLOITATION DIRECTE

OBSERVATIONS

DATE : 11 JANVIER 1999
NUMERO DE L'OBSERVATION : 81033
LA SOCIETE NE CONSERVE AUCUNE ACTIVITE A SON ANCIEN SIEGE

DATE : 16 JUIN 1999
NUMERO DE L'OBSERVATION : 16154
SOCIETE AYANT PARTICIPE A L'OPERATION DE FUSION : DENOMINATION
SANOFI FORME JURIDIQUE SOCIETE ANONYME SIEGE SOCIAL 174 AVENUE DE



E X T R A I T K B I S

EXTRAIT AU 09 SEPTEMBRE 2001

FRANCE 75013 PARIS RCS 732 059 332 RCS PARIS

DATE : 29 JUIN 1999

NUMERO DE L'OBSERVATION : 18854

SOCIETE AYANT PARTICIPE A L'OPERATION DE FUSION : DENOMINATION

SYNTHELABO FORME JURIDIQUE SOCIETE ANONYME SIEGE SOCIAL 22 AVENUE

GALILEE 92350 LE PLESSIS ROBINSON RCS NANTERRE : B 572 140 945

DATE : 27 JUIN 2001

NUMERO DE L'OBSERVATION : 15912

SOCIETE AYANT PARTICIPE A L'OPERATION DE FUSION : DENOMINATION

LABORATOIRES SYNTHELABO FORME JURIDIQUE SOCIETE ANONYME SIEGE

SOCIAL 22 AVENUE GALILEE 92350 NANTERRE RCS B 397 855 750

EXTRAIT DELIVRE A PARIS

LE 11 SEPTEMBRE 2001 SUR 04 PAGES.

LE GREFFIER ,

DROITS DE GREFFE (DECRET 86-1098 DU 10 OCTOBRE 1986) : H.T 0,00 F
T.V.A. 0,00 % : 0,00 F -SOIT TTC 0,00 F

TOUTE REPRODUCTION MEME CERTIFIEE CONFORME, DU PRESENT EXTRAIT, EST SANS VALEUR.

FIN DE L'EXTRAIT

PAGE 04

COMO NOTARIO PERTO (E) DEL CIRCULO
DE BOGOTA, PARA CONSTAR QUE LA
FOTOCOPIA CONCORDA CON EL ORIGINAL
QUE HE TENIDO A LA VISTA

04 FEB 2003

Ar (Convention de La Haye du 5 Octobre 1954)

1. - République Française

Le présent acte a été dressé par

2. - a été signé par

3. - agissant en qualité de

4. - en revêtu du sceau de

ATTESTE

le 9/10/2001

Je suis la Cour d'Appel

Signature

Le mot "ORIGINAL" ci-dessus signifie que vous êtes en présence d'un original émanant du greffe

29
26

TRATADO DE COOPERACION DE PATENTES
PCT
REPORTE DE BUSQUEDA INTERNACIONAL

(PCT Artículo 18 y Reglas 43 y 44)

Registro de referencia del solicitante o agente 1214/MW	PARA FUTURAS ACCIONES ver Notificación o Transmisión del Reporte de Búsqueda Internacional (Forma PCT/ISA/220) así como, donde aplique, el ítem 5 a continuación.	
Solicitud internacional No. PCT/FR 01/03903	Fecha de registro internacional (día/mes/año) 10/12/2001	Fecha de Prioridad (Primera) (día/mes/año) 11/12/2000
Solicitante SANOFI-SYNTHELABO		

Este Reporte de Búsqueda Internacional ha sido preparado por esta Autoridad de Búsqueda Internacional y es transmitido al solicitante según el Artículo 18. Una copia será transmitida a la Oficina Internacional.

Este Reporte de Búsqueda Internacional consta de un total de 3 hojas.

☒ También está acompañado de una copia de cada documento técnico anterior citado en este reporte.

1. Bases del reporte

a. Respecto al lenguaje, la búsqueda internacional se llevó a cabo según la solicitud internacional en el lenguaje en el cual se presentó, a menos que se indique de otro modo en este ítem.

☐ la búsqueda internacional se llevó a cabo según la traducción de la solicitud internacional proporcionada a esta Autoridad (Regla 23.1(b)).

b. Respecto a una secuencia de ácido nucleótico y/o amino revelado en la solicitud internacional, la búsqueda internacional se llevó a cabo según la lista de la secuencia:

☐ contenido en la solicitud internacional en forma escrita.

☐ presentada junto con la solicitud internacional en forma legible por computador.

☐ proporcionada subsiguientemente a esta Autoridad en forma escrita.

☐ proporcionada subsiguientemente a esta Autoridad en forma legible por computador.

☐ se ha proporcionado la afirmación de que el listado de secuencias escrito proporcionado subsiguientemente no va más allá de la revelación en la solicitud internacional según se presentó.

☐ se ha proporcionado la afirmación de que la información registrada en forma legible por computador es idéntica al listado de la secuencia escrita.

2. ☐ Ciertas reivindicaciones no pudieron localizarse (Ver Casilla I).

3. ☐ Falta unidad de invención (ver Casilla II).

4. Respecto al título,

☒ El texto es aprobado según lo presenta el solicitante.

☐ Esta Autoridad ha establecido que el texto se lee así:

5. Respecto al resumen,

☒ El texto es aprobado según lo presenta el solicitante.

☐ Esta Autoridad ha establecido el texto de acuerdo con la Norma 38.2(b), según aparece en el Recuadro III. El solicitante puede, un mes después de la fecha de haber enviado por correo este reporte de búsqueda internacional, presentar comentarios a esta Autoridad.

6. La figura de los dibujos que se publicará con el resumen es la Figura No.

☐ como lo sugirió el solicitante.

☐ porque el solicitante no sugirió una figura.

☐ porque esta figura caracteriza mejor a la invención.

☐ Ninguna de las figuras.

REPORTE DE BUSQUEDA INTERNACIONAL

Solicitud Internacional No.
PCT/FR 01/03903

A. CLASIFICACION DE MATERIA

CIB 7 A61K9/08 A61K47/12 A61K47/40

Según la Clasificación de Patentes Internacional (CPI) o según la clasificación nacional y la CPI

B. CAMPOS BUSCADOS

Documentación mínima buscada (sistema de clasificación seguido de símbolos de clasificación)

CIB 7 A61K

Documentación buscada fuera de documentación mínima hasta donde dichos documentos se incluyan en los campos buscados

Base de datos electrónica consultada durante la búsqueda internacional (nombre de la base de datos y, donde sea práctico, buscar términos usados)

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

C. DOCUMENTOS CONSIDERADOS RELEVANTES

Categoría *	Citación de documento, con indicación, donde sea apropiado, de los textos relevantes	Relevante a la reivindicación No.
A	US 5 985 915 A (MUNOZ ALAIN ET AL) Noviembre 16 de 1999 (1999-11-16) columna 6, línea 24 - línea 49 columna 7, línea 45 - línea 65 ---	1-19
A	VERDUYN SC; VOS MA; LEUNISSEN HD: "Evaluación de los efectos electrofisiológicos agudos de Dronedarona intravenosa" JOURNAL OF CARDIOVASCULAR PHARMACOLOGY, vol. 33, no. 2, 1999, páginas 212-222, XP001024499 página 213, columna 2, línea 44 - línea 62 --- -/-	1-19

☒ En el recuadro C se enumeran más documentos.

☒ En el anexo se enumeran miembros de la familia de patentes.

* Categorías especiales de documentos citados:

'A' documento que define el estado general de la técnica el cual no se considera de relevancia particular

'E' documento anterior pero publicado en o después de la fecha de presentación internacional

'L' documento que puede arrojar dudas sobre reivindicaciones de prioridad o que se cita para establecer la fecha de publicación de otra citación u otra razón especial (según se especifica)

'O' documento que se refiere a una revelación oral, uso, exhibición u otros medios

'T' documento publicado antes de la fecha de presentación internacional pero después de la fecha de prioridad reivindicada

'T' documento posterior publicado después de la fecha de presentación internacional o fecha de prioridad y que no está en conflicto con la solicitud pero citado para entender el principio o teoría que sustenta la invención

'X' documento de relevancia particular; la invención reivindicada no puede considerarse nueva o no puede considerarse que comprende un paso inventivo cuando el documento se toma solo

'Y' documento de relevancia particular; la invención reivindicada no puede considerarse que comprende un paso inventivo cuando el documento se combina con uno o más documentos, siendo dicha combinación obvia para una persona experta en la técnica

'Z' documento miembro de la misma familia de patentes

Fecha de la terminación real de la búsqueda internacional

Abril 17 de 2002

Fecha de envío por correo del reporte de búsqueda internacional

24/04/2002

Nombre y dirección de correo de ISA/US
European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. No. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax No. (+31-70) 340-3016

Funcionario autorizado

Muller, S

REPORTE DE BUSQUEDA INTERNACIONAL

Solicitud Internacional No.
PCT/FR 01/03903

C. (Continuación) DOCUMENTOS CONSIDERADOS RELEVANTES

Categoría *	Citación de documento, con indicación, donde sea apropiado, de los textos relevantes	Relevante a la reivindicación No.
A	MANNING A; THISSE V; HODEIGE D: "SR33589, como un nuevo agente antiarrítmia tipo-amíadaron" JOURNAL OF CARDIOVASCULAR PHARMACOLOGY, Vol. 25, no. 2, 1995, páginas 252-261, XP001024497 página 253, columna 2, línea 1 - línea 18	1-19

TRAITE DE COOPERATION EN MATIERE DE BREVETS

33
30

Expéditeur : L'ADMINISTRATION CHARGÉE DE
LA RECHERCHE INTERNATIONALE

PCT

NOTIFICATION DE TRANSMISSION DU
RAPPORT DE RECHERCHE INTERNATIONALE
OU DE LA DECLARATION

(règle 44.1 du PCT)

Destinataire SANOI-SYNTHELABO A l'att. de Thouret-Lemaître, E 174 Avenue de France FR-75013 PARIS FRANCE

24 AVR. 2002

Date d'expédition (jour/mois/année)	24/04/2002
--	------------

note Hübner

Référence du dossier du déposant ou du mandataire 1214/MW
--

POUR SUITE A DONNER voir les paragraphes 1 et 4 ci-après
--

Demande internationale n° PCT/FR 01/03903
--

Date du dépôt international (jour/mois/année)	10/12/2001
--	------------

Déposant SANOI-SYNTHELABO

1. ☒ Il est notifié au déposant que le rapport de recherche internationale a été établi et lui est transmis ci-joint.

Dépôt de modifications et d'une déclaration selon l'article 19 :

Le déposant peut, s'il le souhaite, modifier les revendications de la demande internationale (voir la règle 48):

Quand? Le délai dans lequel les modifications doivent être déposées est de deux mois à compter de la date de transmission du rapport de recherche internationale; pour plus de précisions, voir cependant les notes figurant sur la feuille d'accompagnement.

Où? Directement auprès du Bureau International de l'OMPI
34, chemin des Colombettes
1211 Genève 20, Suisse
n° de télécopieur: (41-22)740.14.95

Pour des instructions plus détaillées, voir les notes sur la feuille d'accompagnement.

2. ☐ Il est notifié au déposant qu'il ne sera pas établi de rapport de recherche internationale et la déclaration à cet effet, prévue à l'article 17.2a), est transmise ci-joint.

3. ☐ En ce qui concerne la réserve pouvant être formulée, conformément à la règle 40.2, à l'égard du paiement d'une ou de plusieurs taxes additionnelles, il est notifié au déposant que

☐ la réserve ainsi que la décision y relative ont été transmises au Bureau International en même temps que la requête du déposant tendant à ce que le texte de la réserve et celui de la décision en question soient notifiés aux offices désignés.

☐ la réserve n'a encore fait l'objet d'aucune décision; dès qu'une décision aura été prise, le déposant en sera avisé.

4. Mesure(s) consécutive(s) : il est rappelé au déposant ce qui suit:

Peu après l'expiration d'un délai de 18 mois à compter de la date de priorité, la demande internationale sera publiée par le Bureau International. Si le déposant souhaite éviter ou différer la publication, il doit faire parvenir au Bureau International une déclaration de retrait de la demande internationale, ou de la revendication de priorité, conformément aux règles 90bis.1 et 90bis.3, respectivement, avant l'achèvement de la préparation technique de la publication internationale.

Dans un délai de 19 mois à compter de la date de priorité, le déposant doit présenter la demande d'examen préliminaire international s'il souhaite que l'ouverture de la phase nationale soit reportée à 30 mois à compter de la date de priorité (ou même au-delà dans certains offices).

Dans un délai de 20 mois à compter de la date de priorité, le déposant doit accomplir les démarches prescrites pour l'ouverture de la phase nationale auprès de tous les offices désignés qui n'ont pas été élus dans la demande d'examen préliminaire international ou dans une election ultérieure avant l'expiration d'un délai de 19 mois à compter de la date de priorité ou qui ne pouvaient pas être élus parce qu'ils ne sont pas liés par le chapitre II.

Nom et adresse postale de l'administration chargée de la
recherche internationale



Office Européen des Brevets, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 851 epo nl,
Fax: (+31-70) 340-3016

Fonctionnaire autorisé

Jaap Hurenkamp

P

Les présentes notes sont destinées à donner les instructions essentielles concernant le dépôt de modifications selon l'article 19. Les notes sont fondées sur les exigences du Traité de coopération en matière de brevets (PCT), du règlement d'exécution et des instructions administratives du PCT. En cas de divergence entre les présentes notes et ces exigences, ce sont ces dernières qui priment. Pour de plus amples renseignements, on peut aussi consulter le Guide du déposant du PCT, qui est une publication de l'OMPI.

Dans les présentes notes, les termes "article", "règle" et "instruction" renvoient aux dispositions du traité, de son règlement d'exécution et des instructions administratives du PCT, respectivement.

INSTRUCTIONS CONCERNANT LES MODIFICATIONS SELON L'ARTICLE 19

Après réception du rapport de recherche internationale, le déposant a la possibilité de modifier une fois les revendications de la demande internationale. On notera cependant que, comme toutes les parties de la demande internationale (revendications, description et dessins) peuvent être modifiées au cours de la procédure d'examen préliminaire international, il n'est généralement pas nécessaire de déposer de modifications des revendications selon l'article 19 sauf, par exemple, au cas où le déposant souhaite que ces dernières soient publiées aux fins d'une protection provisoire ou à une autre raison de modifier les revendications avant la publication internationale. En outre, il convient de rappeler que l'obtention d'une protection provisoire n'est possible que dans certains États.

Quelles parties de la demande internationale peuvent être modifiées?

Selon l'article 19, les revendications exclusivement.

Durant la phase internationale, les revendications peuvent aussi être modifiées (ou modifiées à nouveau) selon l'article 34 auprès de l'administration chargée de l'examen préliminaire international. La description et les dessins ne peuvent être modifiés que selon l'article 34 auprès de l'administration chargée de l'examen préliminaire international.

Lors de l'ouverture de la phase nationale, toutes les parties de la demande internationale peuvent être modifiées selon l'article 28 ou, le cas échéant, selon l'article 41.

Quand?

Dans un délai de deux mois à compter de la date de transmission du rapport de recherche internationale ou de 16 mois à compter de la date de priorité, selon l'échéance la plus tardive. Il convient cependant de noter que les modifications seront réputées avoir été reçues en temps voulu si elles parviennent au Bureau international après l'expiration du délai applicable mais avant l'achèvement de la préparation technique de la publication internationale (règle 46.1).

Où ne pas déposer les modifications?

Les modifications ne peuvent être déposées qu'auprès du Bureau international; elles ne peuvent être déposées ni auprès de l'office récepteur ni auprès de l'administration chargée de la recherche internationale (règle 46.2).

Lorsqu'une demande d'examen préliminaire international a été/est déposée, voir plus loin.

Comment?

Soit en supprimant entièrement une ou plusieurs revendications, soit en ajoutant une ou plusieurs revendications nouvelles ou encore en modifiant le texte d'une ou de plusieurs des revendications telles que déposées.

Une feuille de remplacement doit être remise pour chaque feuille des revendications qui, en raison d'une ou de plusieurs modifications, diffère de la feuille initialement déposée.

Toutes les revendications figurant sur une feuille de remplacement doivent être numérotées en chiffres arabes. Si une revendication est supprimée, il n'est pas obligatoire de renuméroter les autres revendications. Chaque fois que des revendications sont renumérotées, elles doivent l'être de façon continue (instruction 205.b)).

Les modifications doivent être effectuées dans la langue dans laquelle la demande internationale est publiée.

Quels documents doivent/pourvent accompagner les modifications?

Lettre (instruction 205.b)):

Les modifications doivent être accompagnées d'une lettre.

La lettre ne sera pas publiée avec la demande internationale et les revendications modifiées. Elle ne doit pas être confondue avec la "déclaration selon l'article 19.1)" (voir plus loin sous "Déclaration selon l'article 19.1)").

La lettre doit être rédigée en anglais ou en français, au choix du déposant. Cependant, si la langue de la demande internationale est l'anglais, la lettre doit être rédigée en anglais; si la langue de la demande internationale est le français, la lettre doit être rédigée en français.

La lettre doit indiquer les différences existant entre les revendications telles que déposées et les revendications telles que modifiées. Elle doit indiquer en particulier, pour chaque revendication figurant dans la demande internationale (étant entendu que des indications identiques concernant plusieurs revendications peuvent être groupées), si

- i) la revendication n'est pas modifiée;
- ii) la revendication est supprimée;
- iii) la revendication est nouvelle;
- iv) la revendication remplace une ou plusieurs revendications telles que déposées;
- v) la revendication est le résultat de la division d'une revendication telle que déposée.

Les exemples suivants illustrent la manière dont les modifications doivent être expliquées dans la lettre d'accompagnement:

1. [Lorsque le nombre des revendications déposées initialement s'élevait à 48 et qu'à la suite d'une modification de certaines revendications il s'élève à 51]:
"Revendications 1 à 15 remplacées par les revendications modifiées portant les mêmes numéros; revendications 30, 33 et 36 modifiées; nouvelles revendications 49 à 51 ajoutées."
2. [Lorsque le nombre des revendications déposées initialement s'élevait à 15 et qu'à la suite d'une modification de toutes les revendications il s'élève à 11]:
"Revendications 1 à 15 remplacées par les revendications modifiées 1 à 11."
3. [Lorsque le nombre des revendications déposées initialement s'élevait à 14 et que les modifications consistent à supprimer certaines revendications et à en ajouter de nouvelles]:
"Revendications 1 à 6 et 14 pas modifiées; revendications 7 à 13 supprimées; nouvelles revendications 15, 16 et 17 ajoutées" ou
"Revendications 7 à 13 supprimées; nouvelles revendications 15, 16 et 17 ajoutées; toutes les autres revendications pas modifiées."
4. [Lorsque plusieurs sortes de modifications sont faites]:
"Revendications 1-10 pas modifiées; revendications 11 à 13, 16 et 19 supprimées; revendications 14, 15 et 18 remplacées par la revendication modifiée 14; revendication 17 divisée en revendications modifiées 15, 16 et 17; nouvelles revendications 20 et 21 ajoutées."

"Déclaration selon l'article 19.1)" (Règle 46.4)

Les modifications peuvent être accompagnées d'une déclaration expliquant les modifications et précisant l'incidence que ces dernières peuvent avoir sur la description et sur les dessins (qui ne peuvent pas être modifiés selon l'article 19.1)).

La déclaration sera publiée avec la demande internationale et les revendications modifiées.

Elle doit être rédigée dans la langue dans laquelle la demande internationale est publiée.

Elle doit être succincte (ne pas dépasser 500 mots si elle est établie ou traduite en anglais).

Elle ne doit pas être confondue avec la lettre expliquant les différences existant entre les revendications telles que déposées et les revendications telles que modifiées, et ne la remplace pas. Elle doit figurer sur une feuille distincte et doit être munie d'un titre permettant de l'identifier comme telle, constitué de préférence des mots "Déclaration selon l'article 19.1)"

Elle ne doit contenir aucun commentaire dénigrant relatif au rapport de recherche internationale ou à la pertinence des citations que ce dernier contient. Elle ne peut se référer à des citations se rapportant à une revendication donnée et contenue dans le rapport de recherche internationale qu'en relation avec une modification de cette revendication.

Conséquences du fait qu'une demande d'examen préliminaire international ait déjà été présentée

Si, au moment du dépôt de modifications effectuées en vertu de l'article 19, une demande d'examen préliminaire international a déjà été présentée, le déposant doit de préférence, lors du dépôt des modifications auprès du Bureau international, déposer également une copie de ces modifications auprès de l'administration chargée de l'examen préliminaire international (voir la règle 62.2a), première phrase).

Conséquences au regard de la traduction de la demande internationale lors de l'ouverture de la phase nationale

L'attention du déposant est appelée sur le fait qu'il peut avoir à remettre aux offices désignés ou élus, lors de l'ouverture de la phase nationale, une traduction des revendications telles que modifiées en vertu de l'article 19 au lieu de la traduction des revendications telles que déposées ou en plus de celle-ci.

Pour plus de précisions sur les exigences de chaque office désigné ou élu, voir le volume II du Guide du déposant du PCT.

RAPPORT DE RECHERCHE INTERNATIONALE

(article 18 et règles 43 et 44 du PCT)

Référence du dossier du déposant ou du mandataire 1214/MW	POUR SUITE voir la notification de transmission du rapport de recherche internationale (formulaire PCT/ISA/220) et, le cas échéant, le point 5 ci-après A DONNER	
Demande internationale n° PCT/FR 01/ 03903	Date du dépôt international (jour/mois/année) 10/12/2001	(Date de priorité (la plus ancienne) (jour/mois/année) 11/12/2000
Déposant SANOFI-SYNTHELABO		

Le présent rapport de recherche internationale, établi par l'administration chargée de la recherche internationale, est transmis au déposant conformément à l'article 18. Une copie en est transmise au Bureau international.

Ce rapport de recherche internationale comprend 3 feuilles.

☒ Il est aussi accompagné d'une copie de chaque document relatif à l'état de la technique qui y est cité.

1. Base du rapport

a. En ce qui concerne la langue, la recherche internationale a été effectuée sur la base de la demande internationale dans la langue dans laquelle elle a été déposée, sauf indication contraire donnée sous le même point.

☐ la recherche internationale a été effectuée sur la base d'une traduction de la demande internationale remise à l'administration.

b. En ce qui concerne les séquences de nucléotides ou d'acides aminés divulguées dans la demande internationale (le cas échéant), la recherche internationale a été effectuée sur la base du listing des séquences :

☐ contenu dans la demande internationale, sous forme écrite.

☐ déposée avec la demande internationale, sous forme déchiffrable par ordinateur.

☐ remise ultérieurement à l'administration, sous forme écrite.

☐ remise ultérieurement à l'administration, sous forme déchiffrable par ordinateur.

☐ La déclaration, selon laquelle le listing des séquences présenté par écrit et fourni ultérieurement ne vas pas au-delà de la divulgation faite dans la demande telle que déposée, a été fournie.

☐ La déclaration, selon laquelle les informations enregistrées sous forme déchiffrable par ordinateur sont identiques à celles du listing des séquences présenté par écrit, a été fournie.

2. ☐ Il a été estimé que certaines revendications ne pouvaient pas faire l'objet d'une recherche (voir le cadre I).

3. ☐ Il y a absence d'unité de l'invention (voir le cadre II).

4. En ce qui concerne le titre,

☒ le texte est approuvé tel qu'il a été remis par le déposant.

☐ Le texte a été établi par l'administration et a la teneur suivante:

5. En ce qui concerne l'abrégé,

☒ le texte est approuvé tel qu'il a été remis par le déposant

☐ le texte (reproduit dans le cadre III) a été établi par l'administration conformément à la règle 38.2b). Le déposant peut présenter des observations à l'administration dans un délai d'un mois à compter de la date d'expédition du présent rapport de recherche internationale.

6. La figure des dessins à publier avec l'abrégé est la Figure n°

☐ suggérée par le déposant.

☐ parce que le déposant n'a pas suggéré de figure.

☐ parce que cette figure caractérise mieux l'invention.

☐ Aucune des figures n'est à publier.

A. CLASSEMENT DE L'OBJET DE LA DEMANDE
CIB 7 A61K9/08 A61K47/12 A61K47/40

Selon la classification internationale des brevets (CIB) ou à la fois selon la classification nationale et la CIB

B. DOMAINES SUR LESQUELS LA RECHERCHE A PORTE

Documentation minimale consultée (système de classification suivi des symboles de classement)
CIB 7 A61K

Documentation consultée autre que la documentation minimale dans la mesure où ces documents relèvent des domaines sur lesquels a porté la recherche

Base de données électronique consultée au cours de la recherche internationale (nom de la base de données, et si réalisable, termes de recherche utilisés)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, MEDLINE, CHEM ABS Data

C. DOCUMENTS CONSIDERES COMME PERTINENTS

Catégorie *	Identification des documents cités, avec, le cas échéant, l'indication des passages pertinents	no. des revendications visées
A	US 5 985 915 A (MUNOZ ALAIN ET AL) 16 novembre 1999 (1999-11-16) colonne 6, ligne 24 - ligne 49 colonne 7, ligne 45 - ligne 65	1-19
A	VERDUYN SC; VOS MA; LEUNISSEN HD: (A) "Evaluation of the acute electrophysiologic effects of intravenous Dronedarone..." JOURNAL OF CARDIOVASCULAR PHARMACOLOGY, vol. 33, no. 2, 1999, pages 212-222, XP001024499 page 213, colonne 2, ligne 44 - ligne 62 -/-	1-19



Voir la suite du cadre C pour la fin de la liste des documents



Les documents de familles de brevets sont indiqués en annexe

* Catégories spéciales de documents cités:

- "A" document définissant l'état général de la technique, non considéré comme particulièrement pertinent
- "E" document antérieur, mais publié à la date de dépôt international ou après cette date
- "L" document pouvant jeter un doute sur une revendication de priorité ou cité pour déterminer la date de publication d'une autre citation ou pour une raison spéciale (telle qu'indiquée)
- "O" document se référant à une divulgation orale, à un usage, à une exposition ou tous autres moyens
- "P" document publié avant la date de dépôt international, mais postérieurement à la date de priorité revendiquée

"T" document ultérieur publié après la date de dépôt international ou la date de priorité et n'appartenant pas à l'état de la technique pertinent, mais cité pour comprendre le principe ou la théorie constituant la base de l'invention

"X" document particulièrement pertinent; l'invention revendiquée ne peut être considérée comme nouvelle ou comme impliquant une activité inventive par rapport au document considéré isolément

"Y" document particulièrement pertinent; l'invention revendiquée ne peut être considérée comme impliquant une activité inventive lorsque le document est associé à un ou plusieurs autres documents de même nature, cette combinaison étant évidente pour une personne du métier

"Z" document qui fait partie de la même famille de brevets

Date à laquelle la recherche internationale a été effectivement achevée

17 avril 2002

Date d'expédition du présent rapport de recherche internationale

24/04/2002

Nom et adresse postale de l'administration chargée de la recherche internationale

Office Européen des Brevets, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Fonctionnaire autorisé

Muller, S

C.(suite) DOCUMENTS CONSIDERES COMME PERTINENTS

Catégorie	Identification des documents clés, avec, le cas échéant, l'indication des passages pertinents	no. des revendications visées
A	MANNING A; THISSE V; HODEIGE D: "SR33589, ⁽³⁾ a new amiodarone-like antiarrhythmic agent..." JOURNAL OF CARDIOVASCULAR PHARMACOLOGY, vol. 25, no. 2, 1995, pages 252-261, XP001024497 page 253, colonne 2, ligne 1 - ligne 18 _____	1-19

RAPPORT DE RECHERCHE INTERNATIONALE

Renseignements relatifs aux membres de familles de brevets

Demande internationale No

PCT/FR 01/03903

36

Document brevet cité au rapport de recherche	Date de publication	Membre(s) de la famille de brevet(s)	Date de publication
US 5985915	A	16-11-1999	FR 2746013 A1 19-09-1997
			AU 719358 B2 04-05-2000
			AU 2296297 A 10-10-1997
			CA 2249481 A1 25-09-1997
			CN 1213965 A 14-04-1999
			EP 0796617 A1 24-09-1997
			WO 9734597 A1 25-09-1997
			HU 9902580 A2 28-05-2001
			JP 3253092 B2 04-02-2002
			JP 11507063 T 22-06-1999
			NO 984299 A 17-11-1998
			ZA 9702340 A 18-09-1998

DOCUMENTOS ANEXOS AL REPORTE DE BUSQUEDA INTERNACIONAL

1. US 5 985 915 A
2. XP001024499
3. XP001024497



US005985915A

44
38

United States Patent [19]
Frangin et al.

[11] **Patent Number:** **5,985,915**
[45] **Date of Patent:** **Nov. 16, 1999**

[54] **USE OF ANTIARRHYTHMIC COMPOUNDS
IN THE PREVENTION OF POST-
INFARCTION MORTALITY**

[75] **Inventors:** **Gerald Frangin, Montpellier; Alain
Munoz, Fontaine-les-Dijons, both of
France**

[73] **Assignee:** **Sanoft, Paris, France**

[21] **Appl. No.:** **08/819,863**

[22] **Filed:** **Mar. 17, 1997**

[30] **Foreign Application Priority Data**

Mar. 18, 1996 [FR] France 96 03357

[51] **Int. Cl.⁶ A61K 31/34**

[52] **U.S. CL 514/469**

[58] **Field of Search 514/469**

[56] **References Cited**

U.S. PATENT DOCUMENTS

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

FOREIGN PATENT DOCUMENTS

**WO9509625-
A1 4/1995 WIPO .**

OTHER PUBLICATIONS

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

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

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

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

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

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

[57] **ABSTRACT**

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

30 Claims, 4 Drawing Sheets

74

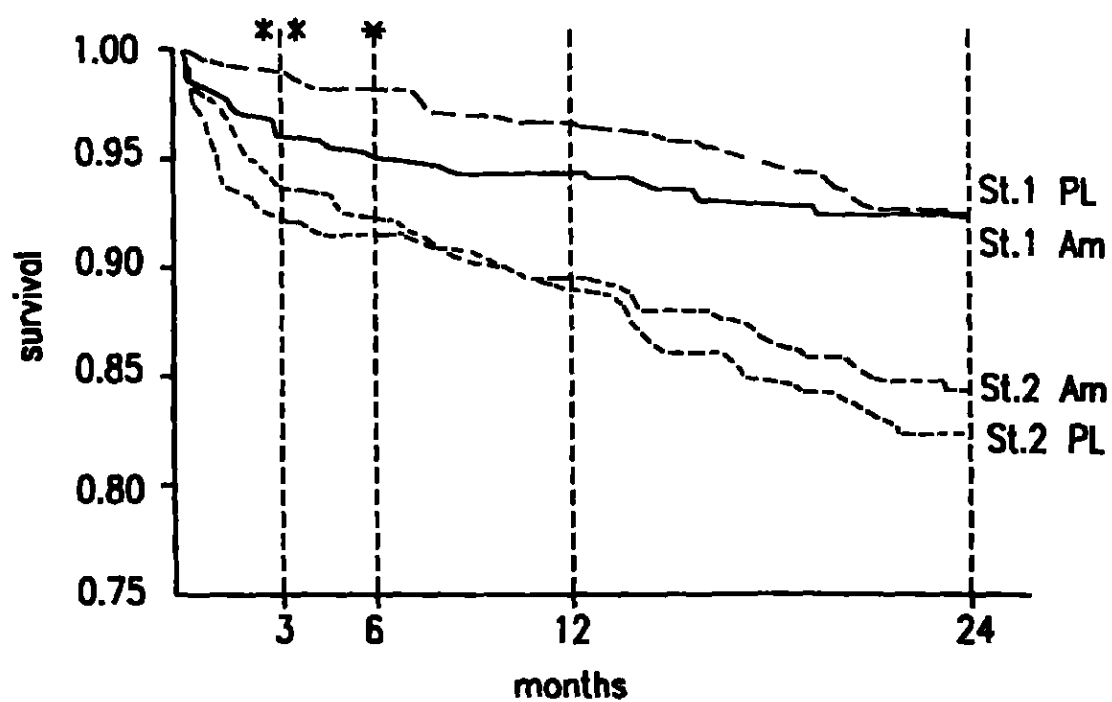


FIG.1

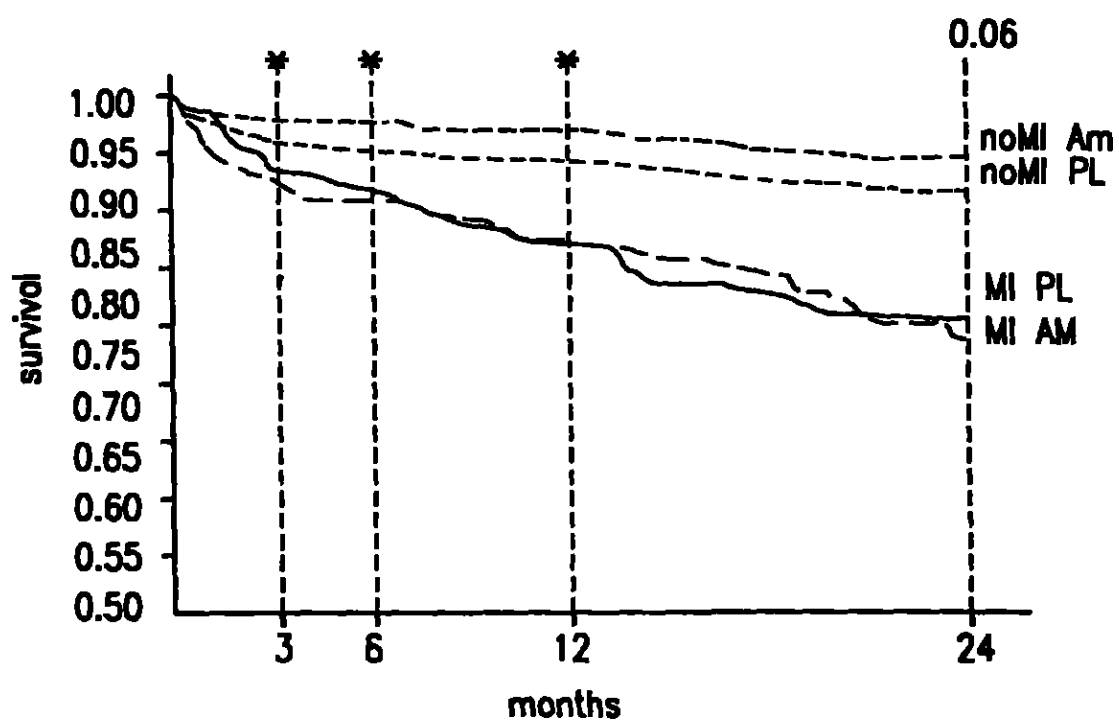


FIG.2

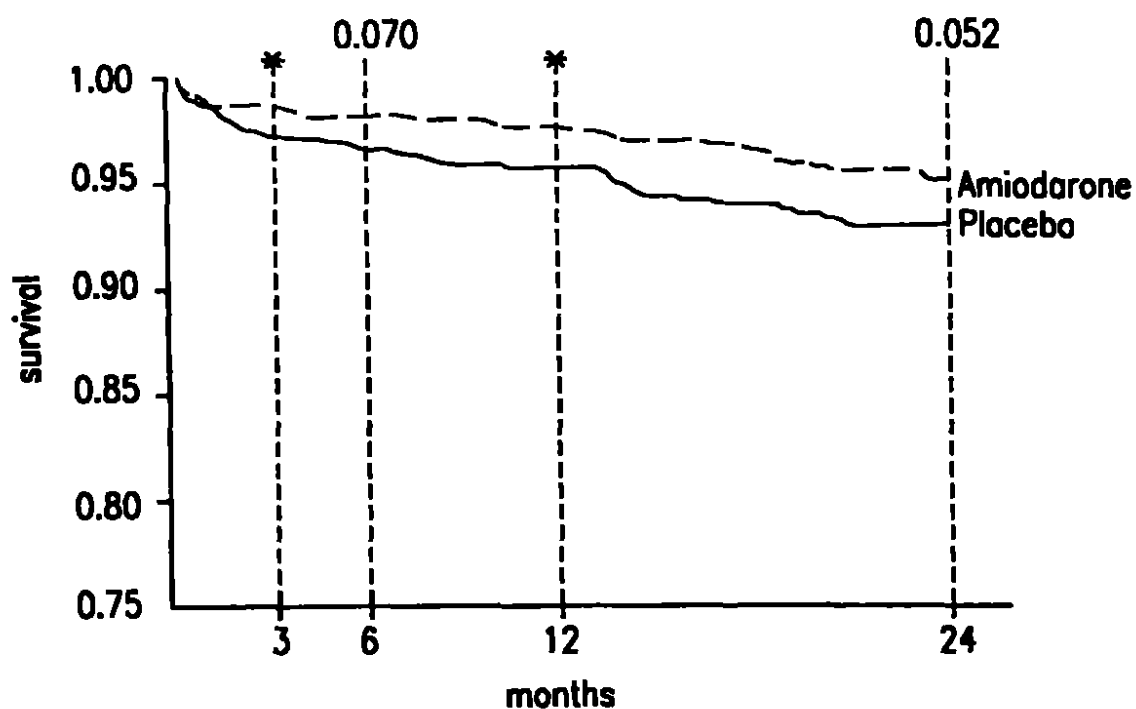


FIG. 3

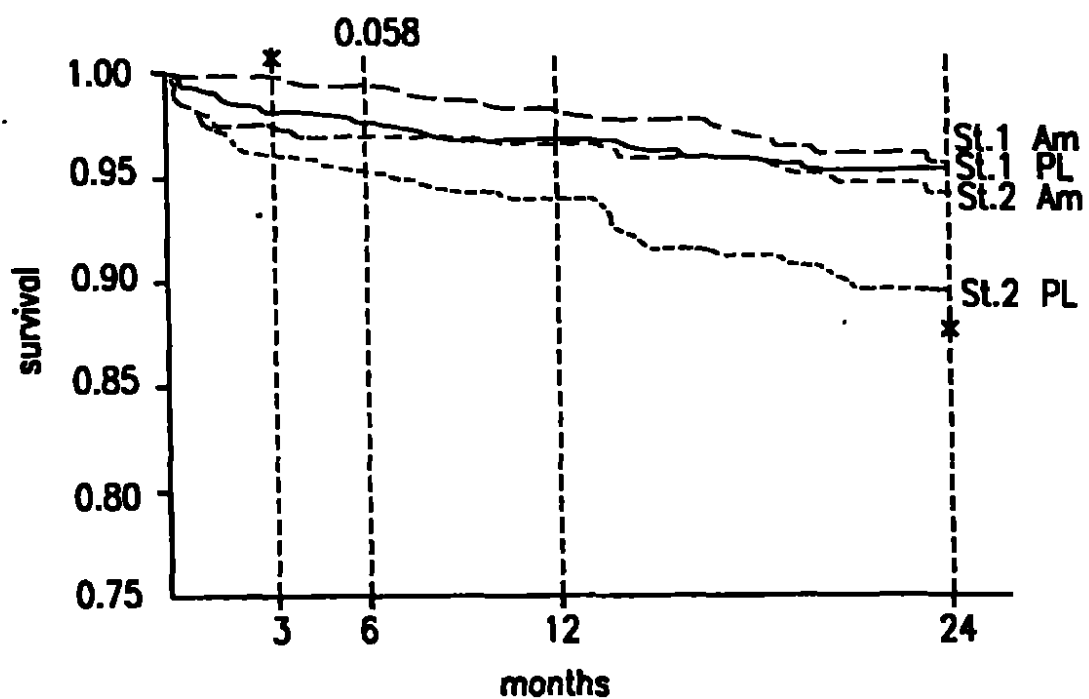


FIG. 4

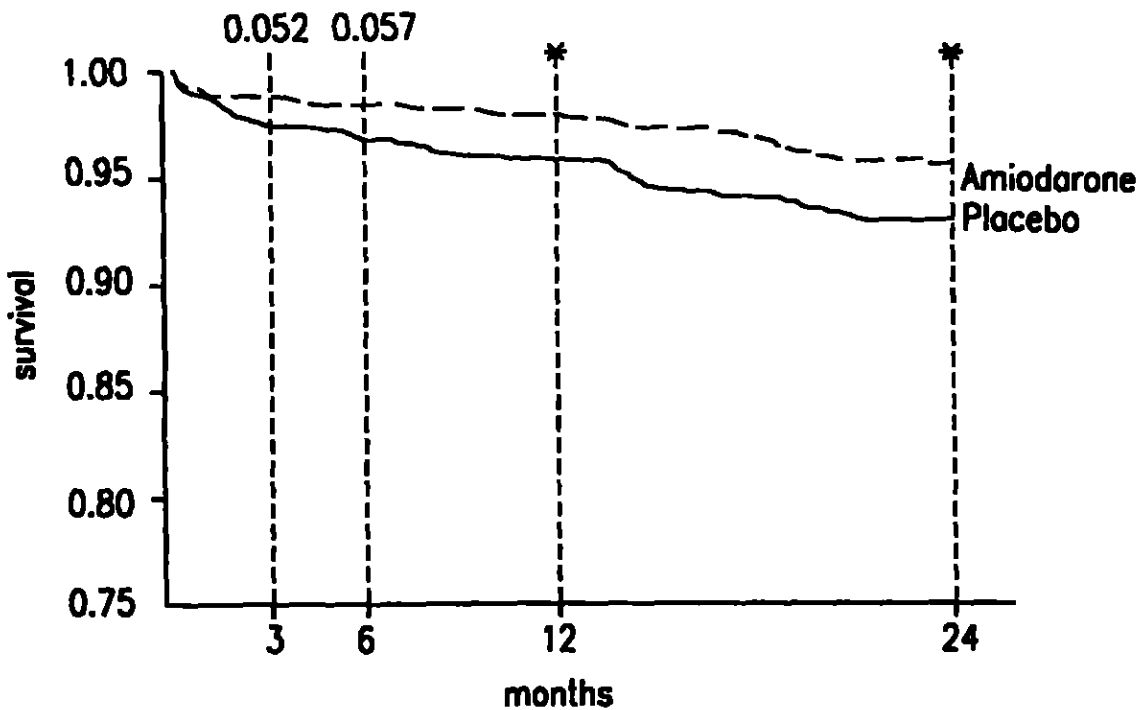


FIG. 5

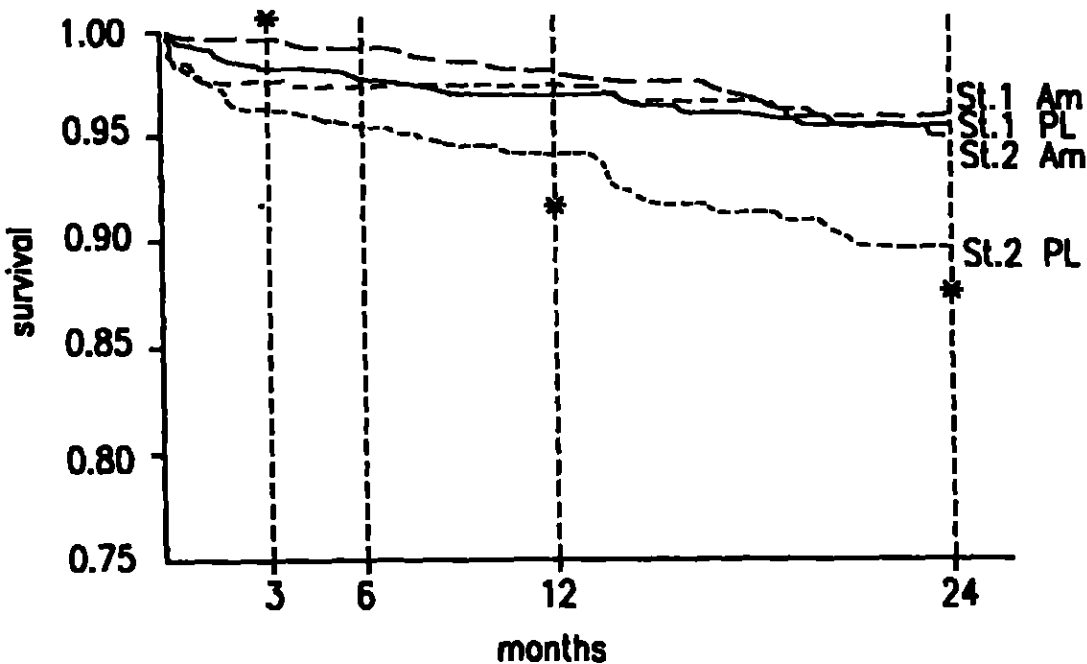


FIG. 6

19

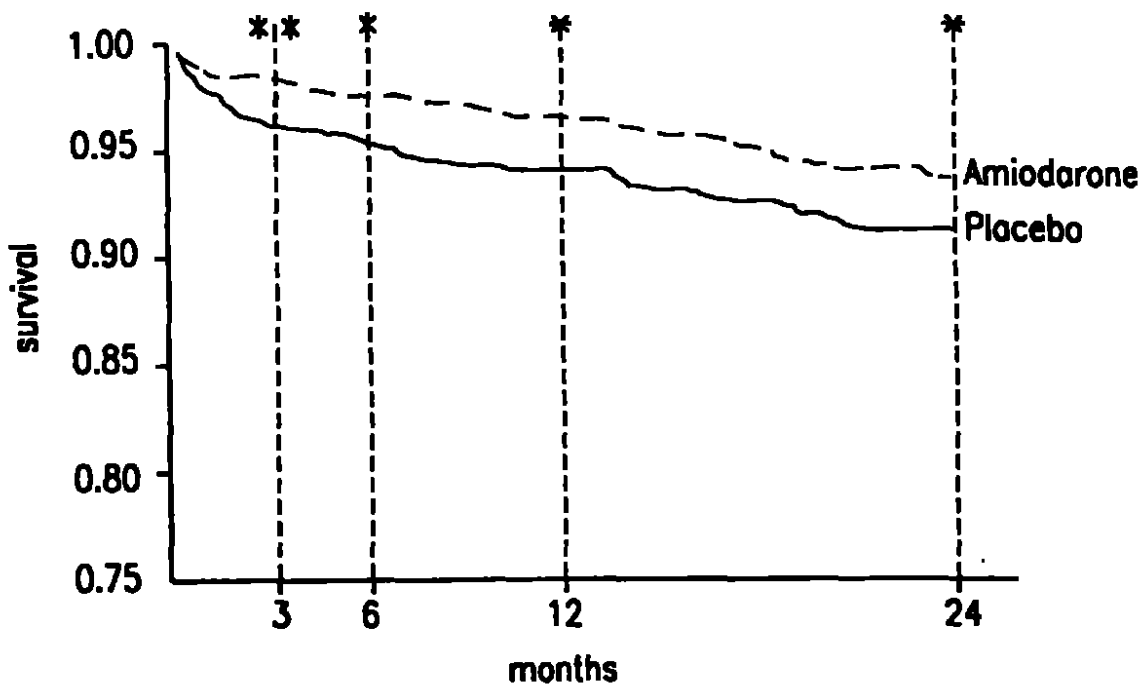


FIG. 7

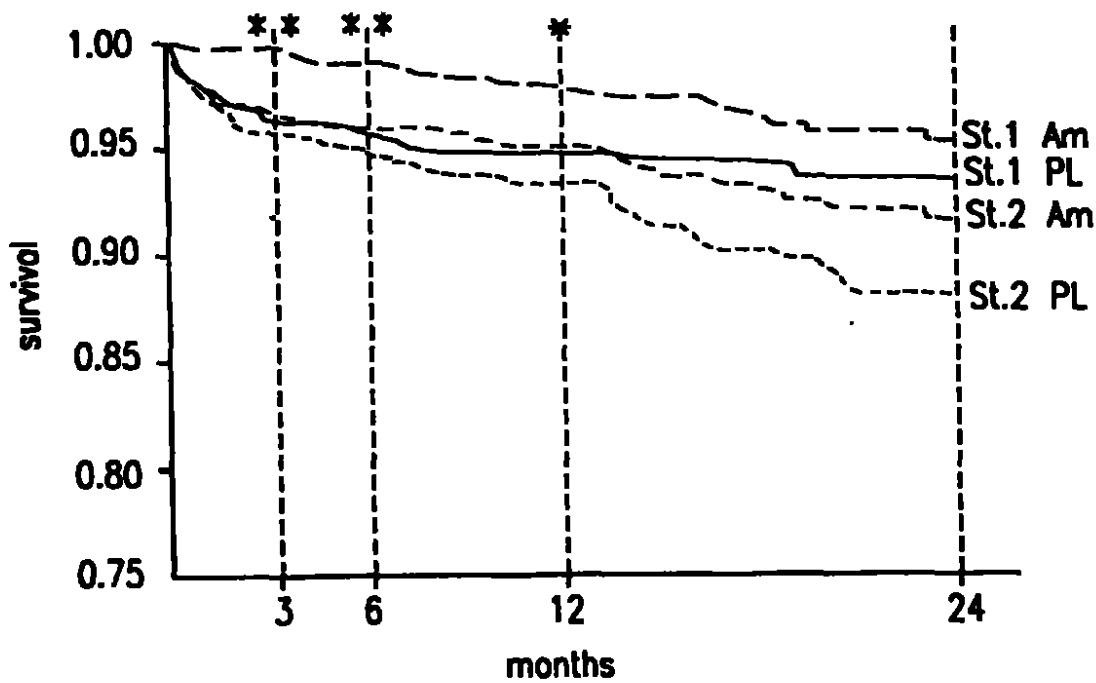


FIG. 8

78

USE OF ANTIARRHYTHMIC COMPOUNDS IN THE PREVENTION OF POST- INFARCTION MORTALITY

The present invention relates, in general, to the use of antiarrhythmic compounds for the prevention of mortality following myocardial infarction.

In particular, the subject of the invention is the use of benzofuran derivatives known for their antiarrhythmic activity, in particular amiodarone, or of pharmaceutically acceptable salts of these derivatives, for the prevention of certain types of mortality following a recent myocardial infarction, especially mortality of cardiac origin, in particular cardiac mortality of arrhythmic origin.

Mortality following myocardial infarction appears at its highest, of the order of 15%, within the first 6 to 12 months following an acute accident, whereas it decreases subsequently and becomes equal to the mortality recorded in stable and chronic coronary disease.

In this context, the extent of the myocardial mass destroyed, which may be represented by the ejection fraction, as well as the ventricular arrhythmias are recognized as major risk factors.

Consequently, a medical therapy intended to prevent mortality following myocardial infarction may prove particularly indicated during the first year after the onset of this cardiac accident although a discussion is possible on the actual duration of this prophylactic therapy.

Numerous studies carried out in patients who have had a myocardial infarction confirm, however, that the left ventricular dysfunction, the ventricular arrhythmias and the extent of the coronary disease contribute independently to the risk of overall mortality and of sudden death, the left ventricular dysfunction being the essential risk factor (Multicenter Postinfarction Research Group—N. Engl. J. Med. 1983; 309: 331–336).

Thus, despite the major advances made over the past few years in the treatment of myocardial infarction, the prognosis remains fairly guarded in patients who show a major impairment of the ventricular function which is reflected by a marked decrease in the ejection fraction at this level.

Although this prognosis is more favorable in patients with an ejection fraction greater than 40%, it deteriorates gradually as this parameter tends towards the critical threshold of 40%. Death, which is often sudden in these patients, is very probably caused in most cases by a ventricular fibrillation degenerating into lethal ventricular tachycardia.

In these cases, it seems, consequently, logical to try to prevent these ventricular disorders by the administration of antiarrhythmic agents. Unfortunately, all attempts to reduce post-infarction mortality with class I antiarrhythmic agents (Vaughan-Williams classification) most widely used has failed especially in patients with arrhythmias or with reduced left ventricular fraction (The CAST Investigators—N. Engl. J. Med. 1989; 321: 406–412).

On the contrary, these antiarrhythmic agents should be contraindicated since instead of reducing the mortality following myocardial infarction, they in fact increase the number of sudden deaths, probably because of their arrhythmogenic effects.

Following these observations, the great majority of cardiologists have been skeptical and even opposed to the concept of prevention of sudden death following myocardial infarction by the administration of antiarrhythmic agents.

Amiodarone, a potent corrector of rhythm disorders widely used in this indication, is capable of substantially suppressing the complex premature ventricular contractions

and the sustained ventricular tachycardia while only exhibiting a little marked negative inotropic effect and being considerably less arrhythmogenic than the class I antiarrhythmics.

However, amiodarone differs from other antiarrhythmic agents in a different mechanism of action: its ability to prolong the duration of the action potential and to extend the refractory period for the myocardial cell places it in the category of Vaughan-Williams class III antiarrhythmics.

While it is perfectly recognized that amiodarone is a beneficial agent in potentially fatal arrhythmias which are often refractory to the other antiarrhythmics, its efficacy has also been evaluated in the prevention of deaths occurring after myocardial infarction.

For example, L. Ceremuzinski et al. (J. Am. Coll. Cardiol. 1992; 20: 1056–1062) have recorded, after administration of amiodarone at the dose of 200 mg/day for one year, a significant reduction in the post-infarction mortality and ventricular arrhythmias in high-risk patients with a contraindication to the prescription of β -blockers whereas in the CAMIAT study (Circulation 1991; 84: 550–557), J. A. Cairns et al. observed, at the dose of 300 to 400 mg/day, a tendency of amiodarone to exhibit a beneficial effect towards especially the total mortality or the mortality of cardiac origin in patients having ventricular extrasystoles after myocardial infarction.

In the BASIS study (J. Am. Coll. Cardiol. 1990; 16: 1711–1718), F. Burkart et al., for their part, studied for one year the effects of amiodarone at the dose of 200 mg/day in myocardial infarction survivors having arrhythmias. However, the beneficial effects recorded must be weighed against a lack of efficacy observed in patients with reduced left ventricular function, that is to say with an ejection fraction of less than or equal to 40%.

The main benefit of this study lies, consequently, in the demonstration of an amiodarone effect on the survival of patients having asymptomatic complex ventricular arrhythmias with preserved left ventricular function (ejection fraction $\geq 40\%$).

Consequently, the left ventricle ejection fraction appears to be more involved in the prognosis of survival of the patient than the ventricular arrhythmias, in agreement with C. S. Chakko et al. (Am. Heart J. 1985; 109: 497–504).

Moreover, clinical trials carried out in patients who have not had myocardial infarction have sometimes highlighted different results.

For example, small preliminary studies undertaken with amiodarone in patients suffering from cardiomyopathies, ventricular arrhythmias or cardiac insufficiency have given contradictory results: Neri et al. (Am. Heart J. 1987; 113: 707–715) recorded an improved survival, Cleland et al. (Br. Heart J. 1987; 58: 572–582) reported a reduced incidence of sudden death whereas Nicklas et al. (Am. Heart J. 1991; 122: 1016–1021) as well as Stewart et al. (Brit. Heart J. 1989; 61: 459–460) observed no improvement.

Likewise, in another study carried out in patients suffering in this case from severe cardiac insufficiency, the GESICA study, H. C. Doval et al. (Lancet 1994; 344: 493–498) showed that amiodarone, at the dose of 300 mg/day, for 2 years, made it possible to obtain a significant reduction in mortality in the treated group compared with the control group whether for sudden death or for mortality due to progressive cardiac insufficiency.

Finally, S. N. Singh et al. have published in N. Engl. J. Med. 1995; 333: 77–82, the results of the C11F-STAT clinical study extending over 45 months with daily doses of 360 mg of amiodarone in patients having asymptomatic

ventricular arrhythmias and suffering from moderate cardiac insufficiency of ischaemic or nonischaemic origin.

Although this compound proved effective for suppressing ventricular arrhythmias and improving ventricular function, this study showed, completely unexpectedly, that amiodarone has no effect, after 2 years, either on sudden death or on the prolonging of the survival of patients having a moderate cardiac insufficiency.

However, it has been possible to reveal a tendency to reduce the mortality in patients with nonischaemic cardiomyopathy (ejection fraction $\geq 40\%$).

Attempts to interpret the apparently contradictory results highlighted in these last two trials have been formulated by G. Breithardt (N. Engl. J. Med. 1995; 333: 121-122) and by S. C. Hammill et al. (Heart 1996; 75: 6-7).

These authors have pointed out that the most significant difference between the two studies lies in the actual nature of the underlying cardiac disease.

In fact, the great majority of patients in the CHF-STAT trial had an ischaemic cardiomyopathy whereas, on the contrary, a majority of patients in the GESICA study suffered from nonischaemic cardiomyopathy.

Consequently, and for this reason, the patients in the CHF-STAT study probably did not benefit from amiodarone. The tendency noted in the BASIS study mentioned above where a lack of efficacy of this compound had been observed in patients with ejection fraction $<40\%$ might therefore be confirmed by these trials.

It may therefore be concluded, following these clinical data, that the underlying cause of cardiac insufficiency may play a predominant role in the determination of a beneficial effect of amiodarone on the prophylaxis of the mortality.

Patent FR 2,626,176 can moreover be mentioned which relates to compositions intended for the treatment of coronary insufficiency by combination of amiodarone and at least one vasodilator and one β -blocker.

According to this patent, amiodarone and isosorbide dinitrate, taken separately, do not show, relative to a control group, a reduction in mortality either at 7 days or at 1 year, whereas the early administration, at the start of infarction, of the isosorbide dinitrate/amiodarone combination, followed by a prolonged administration of this same combination, is thought to reduce the mortality at 1 year in myocardial infarction.

Nevertheless, no comparative result is reported therein, which would make it possible to support this conclusion.

This assertion appears, consequently, purely speculative and all the more doubtful since it no longer appears in patent application WO 90/019176 by the same inventor who describes, subsequently, the same compositions intended for the treatment of coronary insufficiency.

Finally, there may be mentioned patent application WO 95/09625 which relates to the use of amiodarone for the treatment of patients suffering from cardiac insufficiency, whether they carry ventricular arrhythmias or otherwise. Amiodarone is possibly combined therein with other cardioactive agents.

However, no reference is made, in this patent application, to a left ventricular dysfunction as essential factor in the cause of mortality, such that it is totally impossible to deduce or even predict the behavior of amiodarone, combined or otherwise with other cardioactive agents, in the presence of this sole risk factor resulting from a lower left ventricular function.

From the results assembled above, it can be asserted that, to a certain extent, a benefit of amiodarone may be demonstrated on the prevention of mortality following myocardial

infarction or otherwise and this, in patients having rhythm disorders and/or certain forms of cardiac insufficiency.

However, there has never been reported or even published up until now any advantage of amiodarone in the prevention of deaths by early administration of this agent after the acute phase of myocardial infarction, especially in the prevention of mortality of cardiac origin, in particular the cardiac mortality of arrhythmic origin, taking into account, as sole predominant and fatal risk factor, a left ventricular dysfunction which results from a low ejection fraction.

There may be mentioned, however, the publications by A. Munoz (Arch. Mal. Coeur 1991; 94 (II): 67-69) and by J. A. Camm et al. (Am. J. Cardiol. 1993; 72: 95F-98F) which describe a clinical study procedure involving the evaluation of amiodarone as agent for the prevention of mortality following myocardial infarction in patients not having arrhythmias during incorporation into the trial but an impaired left ventricular function.

The study in question requiring several years, no result whatsoever has yet been published which would make it possible to confirm or infirm the hypotheses which serve as basis thereto.

Accordingly, it can be concluded from all the studies reported above, that the behavior of amiodarone in relation to mortality in at-risk patients, whether they are in a post-infarction period or otherwise, is far from being elucidated all the more so since the sometimes surprising and divergent results have been recorded which allow the formulation of only simple suppositions on the still poorly known aspects of this antiarrhythmic.

However, it has now been found that amiodarone and its pharmaceutically acceptable salts are capable of preventing, significantly and with fewer arrhythmogenic effects than class I antiarrhythmics, certain types of mortality especially mortality of cardiac origin, in particular cardiac mortality of arrhythmic origin in patients having, following myocardial infarction, a reduced left ventricular function, that is to say patients with ischaemic cardiomyopathy, without symptomatic rhythm disorders.

Consequently, it can be confirmed that there has been demonstrated for the first time, within the framework of the present invention, the possibility of preventing cardiac mortality of arrhythmic origin, especially sudden death in the post-infarction period, by means of an antiarrhythmic agent, in this case amiodarone or its pharmaceutically acceptable salts, in patients with a major risk factor but without symptomatic arrhythmias.

The observed reduction in cardiac mortality of arrhythmic origin is visualized by a reduction in mortality of arrhythmic origin, especially a reduction in the number of sudden deaths.

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

"Benzofuran derivative with antiarrhythmic activity" designates, within the framework of the present invention, a benzofuran compound selected from those described in patents U.S. Pat. No. 3,248,401, U.S. Pat. No. 5,223,510 and EP 338746 as well as in patent applications WO 88/07996, WO 89/02892, WO 90/02743 and WO 94/29289.

From all these compounds, there may be mentioned for example 2-n-butyl-3-[4-(3-di-n-butylaminopropoxy)]

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

capable of being directly converted to tablets. This powder or this granule may be introduced directly into capsules or gelatine capsules, or preferably they may be converted, by compression, into tablet cores.

By way of example, pharmaceutical compositions may be prepared containing doses of 200 mg of amiodarone hydrochloride for administration by the oral route, for example, in the form of tablets, scored or otherwise, by granulation and compression of the following ingredients:

Example 1

Amiodarone hydrochloride	200 mg
Lactose	96 mg
Maize starch	60 mg
Polyvinylpyrrolidone	12 mg
Anhydrous colloidal silica	2.4 mg
Magnesium stearate	4.6 mg
	375 mg

Example 2

Amiodarone hydrochloride	200 mg
Lactose	71 mg
Maize starch	66 mg
Polyvinylpyrrolidone	6 mg
Anhydrous colloidal silica	2.4 mg
Magnesium stearate	4.6 mg
	350 mg

Likewise, a pharmaceutical composition may be prepared containing 106 mg of dronedarone hydrochloride for oral administration especially in the form of a gelatine capsule:

Example 3

Dronedarone hydrochloride (that is to say 100 mg of dronedarone base)	106 mg
Maize starch	138.5 mg
Talc	50 mg
Anhydrous colloidal silica	1.25 mg
Magnesium stearate	2.5 mg
Lactose	301.75 mg
	500 mg

For a parenteral administration, pharmaceutical compositions may also be prepared containing doses of 150 mg of amiodarone hydrochloride or 10.6 mg of dronedarone hydrochloride, for example in the form of an injectable solution of formulation:

Example 4

Amiodarone hydrochloride	150 mg
Polysorbate 80	300 mg
Benzyl alcohol	60 mg
Water for injection ^{aq}	3 ml

Example 5

Dronedarone hydrochloride (that is to say 10 mg of dronedarone base)	10.6 mg
Mannitol	200 mg
Anhydrous sodium dihydrogen phosphate	130 mg
Water for injection ^{aq}	

^{aq}: sufficient quantity for

During the search for a prophylactic effect on post-infarction mortality, in agreement with the invention, the

active ingredient, more specifically amiodarone or its pharmaceutically acceptable salts, may be administered at daily doses ranging from 100 to 800 mg by the oral route, preferably from 200 to 400 mg.

In the specific case of administration of amiodarone, or its pharmaceutically acceptable salts, by the oral route, daily doses greater than 400 mg, for example doses of 400 to 800 mg, especially doses of 600 to 800 mg, are reserved for treatment of short duration, for example by priming treatments requiring a large loading dose of active ingredient, whereas daily doses of less than or equal to 400 mg, for example doses of 200 to 300 mg, preferably doses of 200 mg are more representative of maintenance doses.

In particular, it is possible to use the following therapeutic scheme which comprises the administration of amiodarone hydrochloride as active ingredient first as a loading dose and then as a maintenance dose, namely:

Priming treatment: 800 mg/day or 4 tablets each containing 200 mg doses of amiodarone hydrochloride for 2 weeks, the treatment starting early after the acute phase of myocardial infarction, for example as early as the 5th day.

Maintenance treatment: 400 mg/day or 2 tablets each containing 200 mg doses of amiodarone hydrochloride for 3 to 4 months and then 200 mg of amiodarone hydrochloride for at least 12 months.

According to another aspect of the invention, the administration of the benzofuran derivative with antiarrhythmic activity or of one of its pharmaceutically acceptable salts may be performed in close, that is to say simultaneous or sequential, association with the administration of at least one additional cardioactive agent so as to reinforce the desired prophylactic effect and/or to treat the underlying cardiac disease.

Consequently, another subject of the invention relates to the use of a benzofuran derivative with antiarrhythmic activity, preferably amiodarone or dronedarone, or of a pharmaceutically acceptable salt of this derivative, for the preparation of pharmaceutical compositions to be administered in simultaneous or sequential association with at least one additional cardioactive agent, for the reduction of mortality of cardiac origin in patients having a reduced left ventricular function following myocardial infarction, without rhythm disorders requiring an antiarrhythmic treatment.

According to this variant, the active ingredient, for example amiodarone, dronedarone or one of their pharmaceutically acceptable salts, may be associated with at least one additional cardioactive agent selected from a diuretic, an angiotensin converting enzyme inhibitor, an angiotensin II inhibitor, a calcium inhibitor, a cardiotonic agent, a β -blocking agent, a nitro derivative and a vitamin K inhibitor.

By way of nonlimiting examples, there will be mentioned hereinafter cardioactive agents which may be associated with the active ingredient in question, these agents being called by their International Nonproprietary Name (INN).

Thus, there may be selected:

the diuretic from furosemide, hydrochlorothiazide, metolazone, amiloride and spironolactone, these compounds being administered at therapeutically active doses chosen between 1 and 200 mg/day,

the angiotensin converting enzyme inhibitor from captopril, enalapril, fosinopril, quinapril, ramipril, lisinopril, cilazapril and perindopril, these compounds being administered at therapeutically active doses chosen between 2 and 150 mg/day,

the angiotensin II inhibitor from irbesartan, losartan, candesartan, valsartan, zolasartan, telmisartan,

~~22~~

eprosartan, these compounds being administered at therapeutically active doses chosen between 1 and 200 mg/day. However, irbesartan represents a preferred angiotensin II inhibitor,

the calcium inhibitor from nifedipine, nicardipine, lacidipine, felodipine, amlodipine, diltiazem and verapamil, these compounds being administered at therapeutically active doses chosen between 1 and 500 mg/day,

the cardiotonic agent from acetyldigitoxin, digitoxin and digoxin, these compounds being administered at therapeutically active doses chosen between 0.1 and 2 mg/day,

the β -blocking agent from timolol, atenolol, pindolol, bisoprolol, acebutolol, propranolol, metoprolol, nadolol, terbutolol, alprenolol, betaxolol, celiprolol and oxprenolol, these compounds being administered at therapeutically active doses chosen between 10 and 500 mg/day,

the nitro derivative from nicorandil, isosorbide mononitrate, isosorbide dinitrate and trinitrin, these compounds being administered at therapeutically active doses chosen between 2 and 200 mg/day,

the vitamin K antagonist from warfarin, acenocoumarole and phenprocoumone, these compounds being administered at therapeutically active doses chosen between 1 and 50 mg/day.

The associations with an angiotensin converting enzyme inhibitor or with an angiotensin II inhibitor represent, however, preferred associations.

However, amiodarone or its pharmaceutically acceptable salts, do not represent the preferred benzofuran derivative with antiarrhythmic activity for the preparation, for example, of a simultaneous association represented by a single administrable unit given its particularly prolonged lifetime compared with the other cardioactive agents which would be associated with it.

The prophylactic efficacy of the benzofuran derivatives with antiarrhythmic activity and their pharmaceutically acceptable salts in relation to post-infarction mortality has been demonstrated using amiodarone hydrochloride, during a double blind (with a triple blind approach) multicentre prospective clinical study with randomization of the patients into 2 defined groups using the left ventricular ejection fraction.

This study, which was spread over a period of several years, was performed on high-risk patients with a deficient left ventricular function after a recent myocardial infarction. It consisted in demonstrating, over a period of 2 years, a reduction in cardiac mortality, cardiac mortality of arrhythmic origin concurrent or otherwise with nonfatal arrhythmic events causing a cardiac arrest and finally a reduction in sudden mortality of arrhythmic origin (sudden death).

CLINICAL STUDY

I. Selection of the patients

The randomization of the patients was performed between the 5th and 21st days following the myocardial infarction. During this period, the following inclusion and exclusion criteria were checked for each patient of both sexes capable of being enrolled in the trial, namely:

Inclusion criteria

- 1) presence of a myocardial infarction
- 2) ejection fraction less than or equal to 40% by standardized radionuclide ventriculography
- 3) age more than 18 years and less than 75 years

A Holter recording was also performed for 24 hours but the results were not retained for inclusion.

Exclusion criteria

- 1) contraindications for amiodarone
- 2) specific status of the patient, especially women of reproductive age, noncardiac or pre-existing disease capable of significantly shortening a survival for 2 years or any condition requiring a treatment with tricyclic antidepressants, phenytoin, lidoflazine, prenylamine or vincamine
- 3) need for an antiarrhythmic therapy other than β -blockers or digitalis at the time of inclusion in the trial
- 4) severe angina not responding to a conventional treatment
- 5) serious cardiac insufficiency not responding to a conventional treatment
- 6) need for a cardiac surgery

Each of the 1486 patients selected according to these criteria were included in the study and randomized into two groups between 5 and 21 days following the myocardial infarction so as to receive either amiodarone hydrochloride or the placebo. These groups were formed on the basis of the ejection fraction, that is to say:

a group of 797 patients having an ejection fraction greater than 30% and equal to or less than 40%, hereinafter "Group I"

a group of 689 patients having an ejection fraction of less than 30%, hereinafter "Group II".

II. Duration and treatment

The trial lasted for 4 years, the period of recruitment being spread over 3 years so that the patients recruited during the first 2 years were treated for 2 years and those recruited during the last year were treated up to the end of the trial. The minimum treatment was, consequently, 1 year. This treatment was introduced according to a double blind design using tablets containing either the placebo or 200 mg of amiodarone hydrochloride, according to the following therapeutic scheme:

a) Loading dose:

800 mg, that is to say 4 tablets/day in two doses for 2 weeks.

b) Maintenance dose:

400 mg, that is to say 2 tablets/day in two doses from the 3rd week for 3 months and 2 weeks.

200 mg, that is to say 1 tablet/day for 20 months.

A co-medication was also introduced, namely: angiotensin converting enzyme inhibitors in 77% of the patients, β -blockers in 44%, vitamin K antagonists in 29%, digoxin in 23%, calcium antagonists in 14%.

Holter recordings performed during the trial, showed that about 40% of the patients had more than 10 ventricular premature beats per hour or 3 consecutive premature beats.

III. Results

The differences in survival recorded were analyzed by the Kaplan-Meyer method (p significant if ≤ 0.05).

By taking into account:

the total mortality in the trial, that is to say the mortality due to any cause whether cardiac, noncardiac or unknown

or the total cardiac mortality, that is to say the mortality due to cardiac causes,

no significant difference was recorded, over a period of 24 months, between the rate of survival in the treated group and

the rate of survival in the placebo group. However, no detrimental effect caused by amiodarone hydrochloride was observed over the period considered. In addition, no significant reduction in total mortality was observed in Groups I and II over the same 24-month period. However, it was possible to demonstrate an early preventive effect of the total mortality in Group I over the period of the first 6 months ($p=0.06$) and especially over the period of the first 3 months ($p<0.05$).

Moreover, no significant effect of reduction in total mortality was observed, compared with the placebo group, over a period of 24 months in patients with one or more previous infarctions.

However, a tendency to prevent total mortality in patients with a first infarction was able to be noted over the same 24-month period ($p<0.05$ over 3 months, $p=0.06$ over 6 months and $p=0.07$ over 12 months).

Other results obtained during this randomized trial are presented below with reference to the accompanying drawings in which:

- a) the abbreviations used have the following meanings:
 "PL" means "placebo"
 "Am" and "amiodarone" mean "amiodarone hydrochloride"
 "St. 1" means "Group I"
 "St. 2" means "Group II"
 "MI" means "one or more previous myocardial infarctions"
 "noMI" means "first myocardial infarction"
 "*" means $p<0.05$
 "**" means $p<0.01$.

BRIEF DESCRIPTION OF THE DRAWINGS

b) FIG. 1 represents the number of patients in Groups I and II surviving, for 24 months, death of cardiac origin.

These results show that amiodarone hydrochloride does not significantly reduce, compared with the placebo group, the rate of mortality of cardiac origin over a period of 24 months in the 2 groups in question. However, an early prophylactic effect was able to be demonstrated during the first 6 months in Group I ($p<0.05$ over 6 months) and more particularly in the first 3 months ($p<0.01$ over 3 months).

c) FIG. 2 represents the number of patients surviving, for 24 months, cardiac death following inaugural infarction.

No significant effect of reduction in mortality of cardiac origin over a period of 24 months in patients with a history of infarction, is observed following this trial and compared with the placebo group. On the other hand, a tendency to prevent mortality of cardiac origin in patients without a history of infarction was able to be detected over the same period of 24 months ($p=0.06$ over 24 months) whereas a significant reduction in this type of mortality was noted over a period of 3 months, 6 months and 12 months ($p<0.05$ over 3, 6 and 12 months).

d) FIG. 3 represents the number of patients surviving cardiac death of arrhythmic origin over a period of 24 months.

The results obtained show a significant reduction in this type of mortality, compared with the placebo group, over a period of 3 months ($p<0.05$), 6 months ($p<0.05$) and 24 months ($p=0.052$).

For example, a 44% reduction in cardiac mortality of arrhythmic origin was obtained at 6 months and 30% at 24 months.

e) FIG. 4 represents the number of patients in Groups I and II surviving, over a period of 24 months, cardiac death

of arrhythmic origin. A significant reduction in this type of mortality, compared with the placebo group over a period of 3 months ($p<0.05$) and 6 months ($p=0.058$) in Group I and over a period of 24 months ($p<0.05$) in Group II, can be deduced from these results.

Thus, a significant prophylactic effect was observed which was even more marked in Group II than in Group I, that is to say in patients with a particularly reduced left ventricular ejection fraction ($<30\%$).

f) FIG. 5 represents the number of patients surviving sudden death of arrhythmic origin over a period of 24 months.

The results obtained highlight a significant reduction in this type of mortality compared with the placebo group ($p=0.052$ over 3 months, 0.057 over 6 months, <0.05 over 12 months and <0.05 over 24 months).

In addition, the following % reduction in this type of mortality was recorded:

- 53% reduction at 3 months
- 48% reduction at 6 months
- 48% reduction at 12 months
- 37% reduction at 24 months

g) FIG. 6 represents the number of patients in Groups I and II surviving, over a period of 24 months, sudden death of arrhythmic origin.

Compared with the placebo, a significant reduction in this type of mortality was recorded, over the period considered, in the two groups having received amiodarone hydrochloride. However, an even more marked reducing effect was noted in Group II ($p<0.05$ over 12 months and over 24 months), that is to say in the group of patients having a highly reduced ejection fraction ($<30\%$).

h) FIG. 7 represents the cumulative number of patients surviving over a period of 24 months, either cardiac death of arrhythmic origin or nonfatal cardiac arrests.

These results demonstrate a significant reduction over a period of 24 months, in this type of event compared with the placebo group ($p<0.01$ over 3 months and $p<0.05$ over 6 months, 12 months and 24 months). In addition, the following % reduction was recorded:

- 59% reduction at 3 months
- 45% reduction at 6 months
- 41% reduction at 12 months
- 28% reduction at 24 months

i) FIG. 8 represents the cumulative number of patients in Groups I and II surviving, over a period of 24 months, either cardiac death of arrhythmic origin or non-fatal cardiac arrests.

In Group II, a tendency to prevent this type of event was noted over a period of 24 months whereas in Group I, a significant reduction in this type of event was obtained with amiodarone hydrochloride compared with the placebo group over a period of at least 12 months ($p<0.01$ over 3 and 6 months and $p<0.05$ over 12 months).

We claim:

1. Method for reducing mortality of cardiac origin, or nonfatal cardiac arrests effected by an arrhythmic event, in a patient having reduced left ventricular function after myocardial infarction, without rhythm disorders requiring antiarrhythmic treatment, comprising administering to said patient an effective amount of one or more active ingredients selected from the group consisting of benzofuran derivatives with antiarrhythmic activity and pharmaceutically acceptable salts, thereof, in combination with one or more pharmaceutically acceptable vehicles.

2. Method according to claim 1, wherein the active ingredient is amiodarone or one of its pharmaceutically acceptable salts.

3. Method according to claim 1, wherein the active ingredient is dronedarone or one of its pharmaceutically acceptable salts.

4. Method according to claim 1, wherein the active ingredient is desethylamiodarone or one of its pharmaceutically acceptable salts.

5. Method according to claim 1, wherein the active ingredient is N-desbutyldronedarone.

6. Method according to claim 1, wherein the active ingredient is in the form of its hydrochloride salt.

7. Method according to claim 1, wherein the active ingredient is amiodarone hydrochloride.

8. Method according to claim 1 for reducing mortality of cardiac origin, wherein said mortality is cardiac mortality of arrhythmic origin.

9. Method according to claim 1 for reducing non-fatal cardiac arrest effected by an arrhythmic event.

10. Method according to claim 8, wherein the cardiac mortality of arrhythmic origin is sudden mortality of arrhythmic origin.

11. Method according to claim 1 in patients having a reduced left ventricular function reflected by an ejection fraction $\leq 40\%$.

12. Method according to claim 11, wherein the ejection fraction is greater than 30% and equal to or less than 40%.

13. Method according to claim 11, wherein the ejection fraction is less than 30%.

14. Method according to claim 1, wherein the active ingredient is administered by the oral, sublingual, nasal, inhaled, parenteral, topical, transdermal, or rectal route.

15. Method according to claim 14, wherein the active ingredient is administered by the oral route.

16. Method according to claim 14, wherein the active ingredient is administered by the parenteral route.

17. Method according to claim 15, wherein from 50 to 600 mg of active ingredient are administered.

18. Method according to claim 16, wherein from 10 to 250 mg of active ingredient are administered.

19. Method according to claim 15, wherein daily doses of 100 to 800 mg of amiodarone or one of its pharmaceutically acceptable salts are administered.

20. Method according to claim 19, wherein daily loading doses of 400 to 800 mg of amiodarone or of one of its pharmaceutically acceptable salts are administered.

21. Method according to claim 19, wherein daily maintenance doses of 200 to 300 mg of amiodarone or one of its pharmaceutically acceptable salts are administered.

22. Method according to claim 21, wherein the daily maintenance dose is 200 mg.

23. Method according to claim 1 further comprising the simultaneous or sequential administration of one additional cardioactive agent.

24. Method according to claim 23, wherein the additional cardioactive agent is selected from the group consisting of a diuretic, an angiotensin-converting-enzyme inhibitor, an angiotensin II inhibitor, a calcium inhibitor, a cardiotonic agent, a β -blocking agent, a nitro derivative, and a vitamin K inhibitor.

25. Method according to claim 24, wherein:

the diuretic is selected from the group consisting of furosemide, hydrochlorothiazide, metolazone, amiloride, and spironolactone;

the angiotensin converting enzyme inhibitor is selected from the group consisting of captopril, enalapril, fosinopril, quinapril, ramipril, lisinopril, cilazapril, and perindopril;

the angiotensin II inhibitor is selected from the group consisting of irbesartan, losartan, candesartan, valsartan, zolasartan, telmisartan, and eprosartan;

the calcium inhibitor is selected from the group consisting of nifedipine, nicardipine, lacidipine, felodipine, amlodipine, diltiazem, and verapamil;

the cardiotonic agent is selected from the group consisting of acetyldigoxin, digoxin, and digoxin;

β -blocking agent is selected from the group consisting of timolol, atenolol, pindolol, bisoprolol, acebutolol, propranolol, metoprolol, nadolol, terbutolol, alprenolol, betaxolol, celiprolol, and oxprenolol;

the nitro derivative is selected from the group consisting of nicorandil, isosorbide mononitrate, isosorbide dinitrate, and trinitrin;

the vitamin K antagonist is selected from the group consisting of warfarin, acenocoumarole, and phenprocoumon.

26. Method according to claim 24, wherein the additional cardioactive agent is selected from the group consisting of an angiotensin-converting-enzyme inhibitor and an angiotensin II inhibitor.

27. Method according to claim 26, wherein the angiotensin II inhibitor is irbesartan.

28. Method according to claim 23, wherein the active ingredient is amiodarone or one of its pharmaceutically acceptable salts.

29. Method according to claim 23, wherein the active ingredient is dronedarone or one of its pharmaceutically acceptable salts.

30. Method according to claim 23, wherein the active ingredient is in the form of its hydrochloride salt.

* * * * *

P.D. 1999 8. 212-222 (11)

Evaluation of the Acute Electrophysiologic Effects of Intravenous Dronedaron, an Amiodarone-Like Agent, with Special Emphasis on Ventricular Repolarization and Acquired Torsade de Pointes Arrhythmias

S. C. Verduyn, M. A. Vos, H. D. M. Leunissen, J. M. van Opstal, and H. J. J. Wellens

Department of Cardiology, Cardiovascular Research Institute Maastricht, Maastricht University, Maastricht, The Netherlands

Summary: In the anesthetized dog with complete chronic AV block (CAVB), we evaluated and compared the acute electrophysiologic effects of dronedarone i.v. (Dron, 2 times 2.5 mg/kg/10 min) and amiodarone i.v. (Amio, 2 times 5 mg/kg/10 min). This canine model with a high sensitivity for acquired torsade de pointes (TdP) provides an ideal substrate to evaluate ventricular repolarization abnormalities. Six ECG leads and two endocardial monophasic action potential (MAP) recordings in the left and right ventricle (LV and RV) were simultaneously recorded to measure QT time, action-potential duration (APD), interventricular dispersion ($\Delta APD = LV_{APD} - RV_{APD}$), early afterdepolarizations (EADs), ectopic beats (EBs), and TdP. Measurements were made at the spontaneous idioventricular rhythm (IVR) and 1,000-ms steady-state pacing. To investigate its short-term antiarrhythmic properties, Dron was given after almokalant (0.12 mg/kg)-induced TdP. Furthermore, in another set of experiments, oral Dron (20 mg/kg, b.i.d) was given for 3 weeks to conscious CAVB dogs. Dron, i.v., shortened ventricular repolarization

(QT, 435 ± 60 to 360 ± 55 ; LV_{APD} , 395 ± 75 to 335 ± 60 ms; $p < 0.05$), whereas IVR and ventricular effective refractory period (VERP, 225 ± 30 to 230 ± 30 ms) remained similar. Therefore the VERP/QT ratio increased $.55 \pm 0.04$ to 0.61 ± 0.03 ; $p < 0.05$). Similar results were obtained with Amio, i.v.. Almokalant-induced TdP was characterized by an increased repolarization duration, ΔAPD , and EADs. Dron, i.v., suppressed the EADs, EBs, and TdP by a reduction and homogenization of repolarization (LV_{APD} , 505 ± 110 to 455 ± 80 ms, and ΔAPD , 110 ± 55 to 65 ± 40 ms). Long-term oral Dron increased the PP interval, CL-IVR, and QT₁₀ time. In contrast to oral treatment, Dron i.v. shortens ventricular repolarization parameters, resulting in suppression of EAD-dependent acquired TdP. The increased VERP/QT ratio after Dron i.v. may indicate an important second antiarrhythmic property. **Key Words:** Dronedaron—Amiodarone—Almokalant—Dog—Electrophysiology—Repolarization arrhythmias—Triggers activity—Early afterdepolarizations—Monophasic action potentials—Ventricle.

With the exception of β -blockers (1,2), the beneficial effect of pharmacologic treatment of life-threatening ventricular arrhythmias has been questioned by the outcome of several multicenter trials (3–10). The increased mortality in the CAST trial (3) after class I drugs and in the SWORD trial (with the class III agent *d*-sotalol; 5) were ascribed to an increased prevalence of lethal ventricular arrhythmias related to an interaction with ischemia (3) or, in case of *d*-sotalol, to acquired torsade de pointes arrhythmias (TdP; 5).

In regard to amiodarone, both the oral (1,2) and the intravenous (i.v.; 11,12) administration were proven beneficial in the prevention and suppression of life-threatening ventricular arrhythmias. Classification of amiodarone

is difficult because it possesses effects belonging to a classes of the Vaughan Williams classification, including β -blockade (11–14). The picture is further complicated because the short-term electrophysiologic action differs from the long-term effects (e.g., 13,15). Specifically, its class III action (prolongation of ventricular repolarization) seems to emerge after several days to weeks of therapy (13,15).

In comparison to other antiarrhythmic agents, the Td incidence after both long-term i.v. and oral amiodarone is very low (11,12,16). Sometimes amiodarone even replaces the proarrhythmic drug (17–19) or is given as antidote for acquired TdP (19,20). However, amiodarone possesses other serious (dose-dependent) side effects.

Received December 12, 1997; revision accepted July 24, 1998.
Address correspondence and reprint requests to Dr. M. A. Vos at Department of Cardiology, Cardiovascular Research Institute Maastricht,

Maastricht University, P.O. Box 5800, 6200 AZ Maastricht, The Netherlands.

(21,22), which are (partly) related to the presence of iodine in its structure, causing thyroid dysfunction. These side effects limit its general use, with a discontinuation of 40% (2).

A drug with the same electrophysiologic characteristics but without these negative side effects could certainly be of value. Dronedarone, a newly developed agent, is structurally related to amiodarone (Fig. 1), but does not possess the iodine groups. A few short-term electrophysiologic studies in large animals were performed, showing similar effects as amiodarone i.v., although obtained at lower doses of dronedarone (23-25).

It was the aim of this study to evaluate the short-term electrophysiologic effects of dronedarone i.v. with special emphasis on ventricular repolarization and repolarization-related arrhythmias. Therefore the effects of dronedarone, i.v., were tested in the dog with chronic complete AV block (CAVB), a model known for its a high sensitivity for (acquired) TdP arrhythmias (26-29). Moreover, these effects were compared with (a) amiodarone, i.v., and (b) the pure class III drug almokalant. Finally, the effect of long-term treatment of oral dronedarone was tested in conscious CAVB dogs.

METHODS

All experiments were performed in accordance with the Guide for the Care and Use of Laboratory Animals, NIH 86-23, revised 1996, and were approved by the Committee for Experiments on Animals of the Maastricht University, Maastricht, the Netherlands.

General

For these experiments, 18 mongrel dogs were selected based on age (adult) and size (body weight of >20 kg; mean, 25 ± 4 kg), but not on race or gender. In a preliminary surgery, a right-sided thoracotomy was performed under general anesthesia (see later) to induce CAVB by injection of 37% formaldehyde into the atrioventricular junction (28). During the same session, an epicardial pacing electrode (Bakken Research Center, Medtronic, Mass-

trich, The Netherlands) was inserted at the apex of the left ventricle. Thereafter, the thorax was closed, and the wire was exteriorized through the back of the neck of the dog.

For the i.v. administration of drugs, 13 anesthetized dogs with CAVB (22 weeks) were used. After overnight fasting, anesthesia was induced by (a) premedication, i.m. (1 ml/3 kg: 10 mg oxydron, 1 mg acepromazine, and 0.5 mg atropine), and (b) sodium pentobarbital (20 mg/kg, i.v.). The dogs were artificially ventilated through a cuffed endotracheal tube by using a mixture of oxygen, nitrous oxide, and halothane (vapor concentration, 0.5-1%) by a respirator (Pulmonat, Dräger, Lübeck, Germany). Ventilation was controlled by continuous reading of the carbon dioxide concentration in the expired air. A thermal mattress was used to maintain adequate body temperature. Because the animals are used over the long term, proper care was taken before and after the anesthesia experiments, including antibiotics (1,000 mg ampicillin) and analgesics (0.015 mg/kg, i.m. buprenorphine). A temporary external ventricular pacemaker (VVT) was given after the CAVB operation and after anesthesia to speed recovery. Ventricular pacing (50 beats/min) was discontinued after a maximum of 24 h.

In five dogs, oral dronedarone (20 mg/kg/twice daily) was administered during their meals for a period of 3 weeks, starting at 6 weeks of CAVB. These dogs were tested while conscious.

Study design: i.v. administration of drugs

In seven dogs, the dose-dependent, short-term, electrophysiologic effects of dronedarone were compared with a single dose of almokalant. For this purpose, the dogs were studied in a randomized crossover design in which the experiments were performed ≥1 week apart. Almokalant was administered at 4 ± 2.4 weeks CAVB, and dronedarone, at 5 ± 2.6 weeks CAVB. Four dogs received almokalant in the first experiment; the other three received dronedarone in the first experiment. Amiodarone was administered to four dogs (8 ± 2.6 weeks CAVB), of which two dogs took part in the previous series, extending their number of experiments to three. The remaining two did not receive dronedarone or almokalant in an earlier experiment.

When we analyzed the electrophysiologic data, it became clear that dronedarone shortened all ventricular repolarization parameters. Therefore, we evaluated the antiarrhythmic properties of dronedarone in a second set of dogs (n = 4), in which almokalant was used to induce TdP.

Drug administration and determination of dosage

All i.v. drugs were administered through a cannula in the cephalic vein.

Dronedarone and amiodarone were provided by Sanofi, France. The dose of dronedarone (2.5 mg/kg/10 min) and amiodarone (5 mg/kg/10 min) was based on a previous study performed in sinus rhythm dogs (23), in which it was reported that this single dose had the most pronounced effects on QT time and ventricular effective refractory period (VERP). A further increase in these repolarization parameters was reported with the second dose of dronedarone (23). Before each experiment, dronedarone or amiodarone was weighed and dissolved in polyethylene glycol (PEG) 400 and distilled water (3:1). This mixture was placed in a water bath at 70°C until all drug was dissolved and the solution was clear. Before the solution was intravenously administered to the dog, it was cooled to 37°C. A second bolus of dronedarone (2.5 mg/kg/10 min) or amiodarone (5 mg/kg/10 min) was administered 65 min after the start of the first bolus.

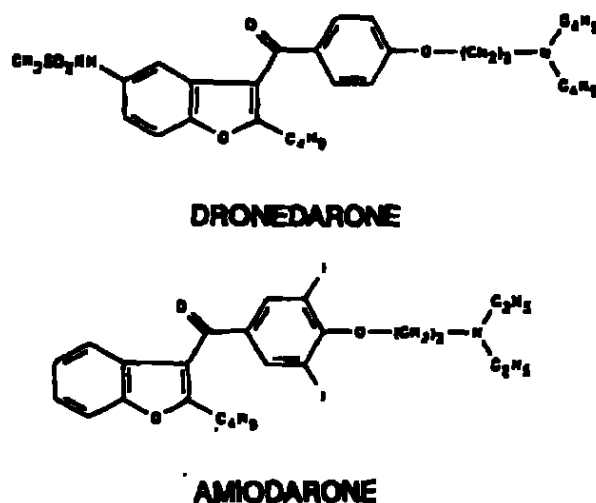


FIG. 1. Chemical formula of dronedarone and amiodarone.

Almokalant, [4-[3-ethyl(3-propylsulfinyl)propyl]amino]2-hydroxy-propoxybenzonitrile, was provided by Astra Sweden. The dose of almokalant (0.12 mg/kg/10 min) was based on previous experiments (29) in which we documented an incidence of 80% spontaneous TdP. Almokalant was freshly prepared by dilution of a stock solution of 1–0.01 mmol with saline.

Electrophysiologic measurements in relation to i.v. drug administration

Six surface electrocardiographic leads and two endocardial monophasic action potential (MAP) signals were simultaneously registered and stored on hard disk. The MAP catheters (Franz combination catheter, EPT 1650, Mountain View, CA, U.S.A.) were randomly placed in each ventricle and used as described previously (27) to visualize the action potential and to record early afterdepolarizations (EADs). MAP recordings had to fulfill the following criteria: amplitude >15 mV, and smooth contour and equal duration in consecutive beats during control. The cycle length (CL), the QT time, the duration of the action potential of the left (LV_{APD}) and right ventricle (RV_{APD}) and the interventricular dispersion (Δ action-potential duration (ΔAPD) defined as $LV_{APD} - RV_{APD}$) were measured during idioventricular rhythm (IVR) to assess the effect of the drugs on ventricular repolarization. Furthermore, at the atrial level, the CL of the sinus node (PP interval) was monitored.

In the dronedarone and amiodarone experiments, the QT time was also measured during a steady-state paced cycle length (PCL) of 1,000 ms. In addition, the VERP was determined at 2 times diastolic threshold by giving an extrastimulus in steps of 5 ms, starting within the refractory period of the basic rhythm (30). Steady state was reached after 5 min of continuous pacing. The PCL of 1,000 ms was chosen to correct for the reported bradycardic effect of these drugs in sinus rhythm dogs (23). Because the site of the impulse formation of the IVR may change (after medication), a paced QRS complex has the advantage of a similar QRS during all stages of the protocol, which facilitates the ability to assess the effect of dronedarone and amiodarone on intraventricular conduction (QRS width) and repolarization parameters.

In all experiments, measurements were performed at baseline and after the complete dose of each drug was injected (10 min). The dronedarone and amiodarone experiments had some additional measurements during IVR: at 25 min, at 40 min, right before the second bolus ($t = 65$), at the end of the second dose ($t = 75$), and at 90 and 110 min. Ventricular pacing with a CL of 1,000 ms was started at 25 and 55 min after each dose of these drugs.

In the antiarrhythmic experiments with dronedarone ($n = 4$), all measurements were done at baseline, after almokalant (i.e., immediately before dronedarone), and after 10 min of dronedarone during spontaneous IVR.

Proarrhythmic parameters

The following proarrhythmic parameters were monitored before and after drug administration: (a) changes in the QT(U) wave morphology (like amplitude, direction) before and directly after pacing (31), (b) the appearance of EADs on the MAPs, (c) occurrence of (triggered) ectopic beats (EBs), and (d) the induction of TdP, either spontaneously or after programmed electrical stimulation (PES). Appearance of acquired TdP in this model is associated with nonhomogeneous lengthening of ventricular repolarization, which is reflected in ΔAPD (27,29). The necessity of PES to induce TdP is related to the

lack of spontaneously occurring (multiple) EBs, which will increase the magnitude of ΔAPD .

A detailed description of the protocol used to induce TdP by pacing has been published (26). In short, specific pacing protocols mimicking the short/long/short sequence are delivered during IVR under baseline conditions. When no spontaneous TdP appears within 15 min after the start of the almokalant infusion, PES will be repeated. In case of dronedarone and amiodarone, PES was performed 45 min after the start of drug administration, because it was reported that the maximal effect on QT time is reached then (23).

TdP shows a very specific undulating pattern of the QRS complexes. This arrhythmia often terminates spontaneously, but can also degenerate into ventricular fibrillation (VF). A dog was called inducible for TdP when such an arrhythmia consisting of at least five beats (a) occurred spontaneously (23 times), or (b) was induced 23 times by using the same pacing mode or both. When it lasted >10 s or when it deteriorated in VF, cardioversion was applied through patches on the thorax, which were placed in advance. In this model, dogs show a very reproducible response to drugs over weeks (26), allowing the comparison of different medications.

Oral administration of dronedarone

In five dogs, oral treatment with dronedarone (20 mg/kg/twice a day) was started in week 6 of CAVB (in the morning of day 43) and continued for 3 weeks. These dogs were trained to have frequent awake electrophysiologic measurements. Dogs had two control ECGs 1 week apart. After this, ECG recordings were made at day 43 (i.e., 6 h after the first oral dose), day 46, day 49, and thereafter every week to monitor changes in QT, CL-IVR, and PP.

Data analysis

All ECG parameters were measured by using a custom-made computer program with a resolution of 2 ms and adjustable gain and time scale. All electrophysiologic data reported are the mean of five consecutive (single) beats.

Statistics

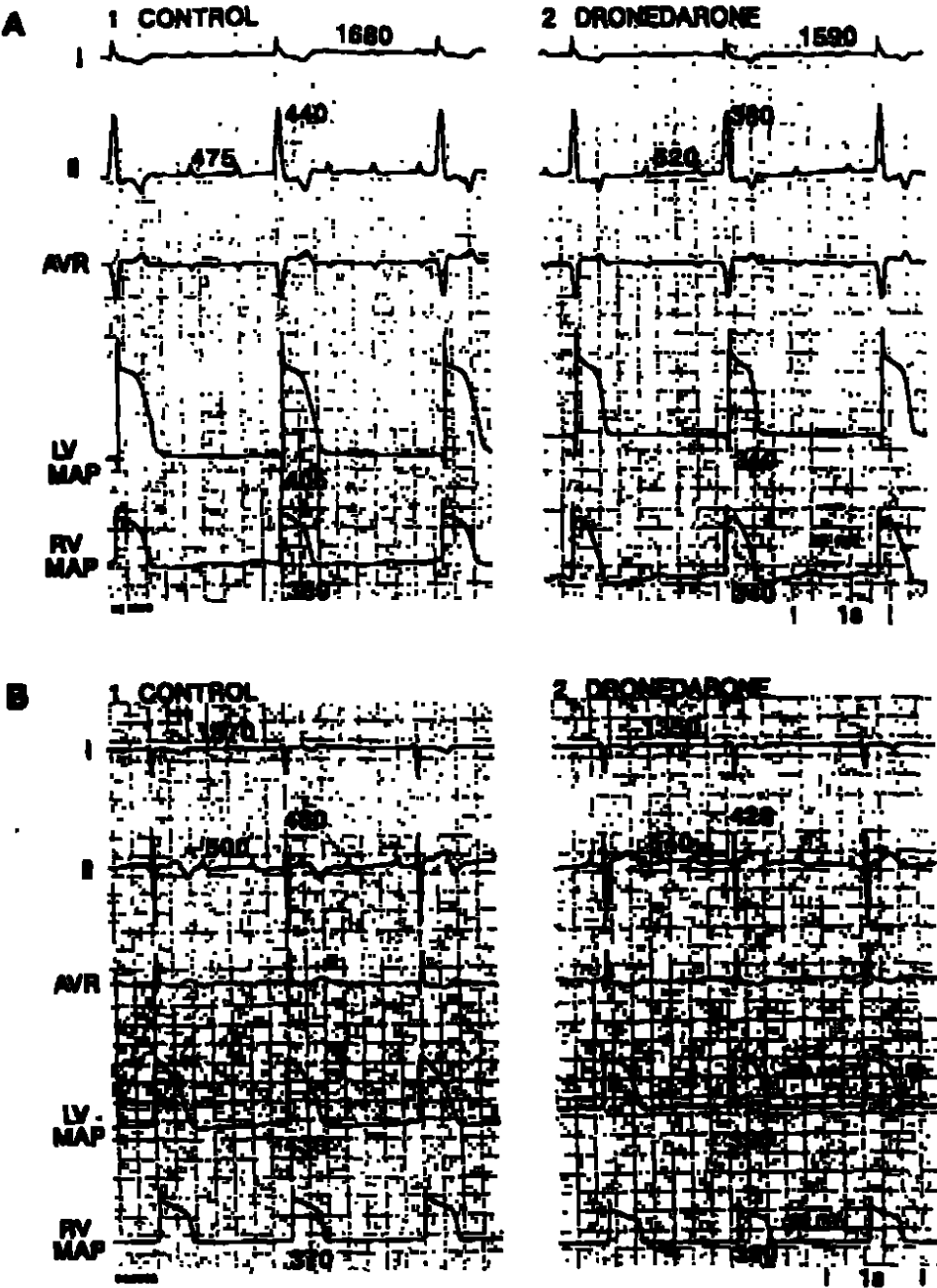
Multiple treatment comparisons were made by using a Friedman two-way analysis of variance (ANOVA) test; if it was significant, it was followed by a Wilcoxon matched-pairs signed-ranks test. Single effects were analyzed with a paired t test. A χ^2 test was used when the data were presented as percentages (32). Values of $p < 0.05$ were considered significant. Data are expressed as mean $\pm$ standard deviation (SD), unless otherwise stated.

RESULTS

Electrophysiologic characteristics of the CAVB dog

In Fig. 2 (A1), a representative example of an ECG of a dog with CAVB is shown. Atrial (PP) and ventricular activation are dissociated, allowing separate analysis of the atrial and ventricular parameters. The PP interval is 475 ms, and the CL-IVR is 1,680 ms. The CL-IVR can originate from several sites in the ventricles; in this case a right ventricular origin seems to be indicated based on the QRS morphology. In lead II, a negative T wave concludes the recording. In a few of the dogs with CAVB, repolarization abnormalities are present at baseline, as evi-

FIG. 2. Electrophysiological effect of the first dose of dronedarone (2.5 mg/kg) in two dogs. Three ECG leads are presented together with the signals of the monophasic action potential in the left (LV MAP) and right ventricle (RV MAP), at a paper speed of 25 mm/s. A: In the left panel (A1), a representative example is shown of a normal baseline situation in a complete AV block (CAVB) dog having a cycle length of the idioventricular rhythm (CL-IVR) of 1,680 ms, a QT time of 440 ms, a PP interval of 475 ms, and an interventricular dispersion of 45 ms ($\Delta APD = 405$ (LV_{APD}) - 360 (RV_{APD}) ms). After dronedarone (A2), the CL-IVR is similar and the PP has prolonged, whereas the QT time has shortened to 380 ms, like both APDs. The difference between the left and right ventricle has completely disappeared; homogenization of repolarization. B: In the left panel (B1), the ECG is shown of a CAVB dog with preexistent repolarization abnormalities under baseline circumstances. The QT time is 480 ms, and the PP interval is 500 ms. Note the presence of a TU wave complex in lead II, indicative for a nonuniform repolarization, which is represented in a ΔAPD of 80 ms: 430 (LV_{APD}) - 370 (RV_{APD}) ms. After dronedarone (B2), the CL-IVR and the PP interval respond as in panel A. However, now there is also a clear normalizing effect of dronedarone on the QT(U) wave structure concomitant with a larger decrease in the LV_{APD} than the RV_{APD}, resulting in decreased ΔAPD .



lenced by a biphasic TU wave and a more pronounced interventricular dispersion in the second example (B1).

Electrophysiologic effects of dronedarone i.v.

Dronedarone did not alter the CL-IVR but shortened the repolarization parameters 10 min after the start of the drug (Table 1 and Figs. 2 and 3). Both the QT time and LV_{APD} decreased significantly, whereas RV_{APD} and ΔAPD had a tendency to shorten (Fig. 2), but this did not reach significance (Table 1). At the atrial level, the PP interval increased from 500 ± 70 to 575 ± 120 ms after the first bolus ($p < 0.05$), reaching the maximal value at 40 min (Fig. 3A).

At the 1,000-ms steady-state paced rhythm (Table 2), no effect was observed on intraventricular conduction, as evidenced by a similar QRS width. However, the decrease in QT time (nonsignificant) was not associated by a decrease in VERP (Table 2), resulting in a significantly increased VERP/QT ratio from 0.55 ± 0.04 to 0.60 ± 0.04 (Table 2).

The second dose decreased the ventricular parameters of ventricular repolarization further, resulting in a shorter QT time than the 10-min value of the first dosage, whereas the PP interval increased further to 620 ± 65 ms at 25 min. Also with the second dose, a different temporal effect was indicated: maximal decrease of repolariza-

29

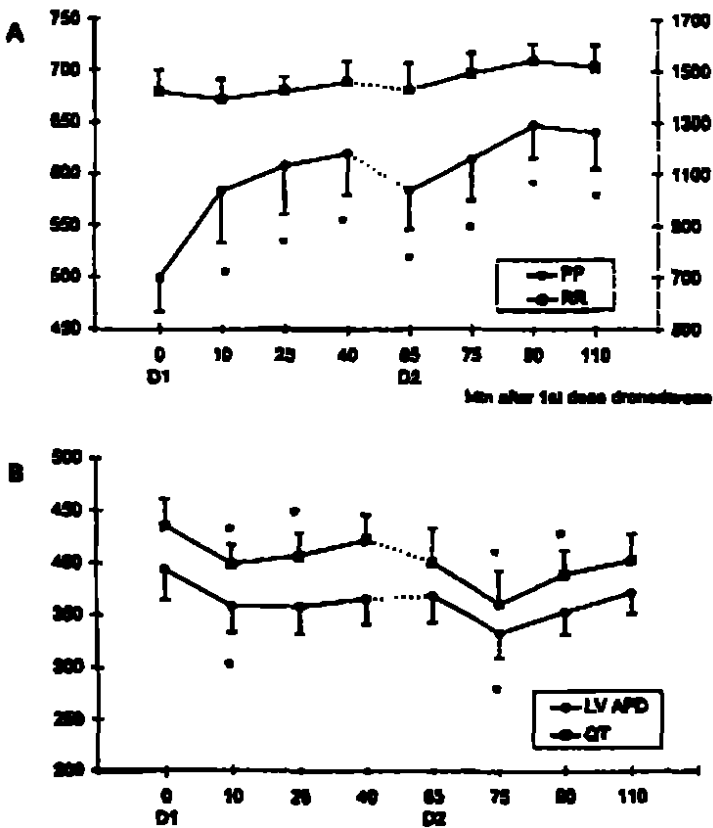


FIG. 3. Temporal effect of dronedarone on heart rate and repolarization. The time-dependent relation of the electro-physiologic parameters is depicted (same abbreviations as Fig. 1). The X axis represents the time after the start of administration of the first dose of dronedarone (D1); at 65 min, the second dose of dronedarone (D2) is started. The asterisk denotes a difference with D1. At the Y axis, the different parameters are denoted in ms. A: The PP interval and the CL-IVR are shown at the left (PP) and right Y axis; the CL-IVR in time does not alter, whereas the PP increases significantly, with a maximal effect reached at 40 min after each dose. B: The LV_{APD} and QT time are depicted; in contrast to the PP interval, the maximal effect of dronedarone on these repolarization parameters is obtained at 10 min after each dose.

tion at 10 min, whereas the maximal increase in PP interval was observed at 25–40 min (Fig. 3).

Electrophysiologic effects of amiodarone i.v.

Baseline values were comparable with the baseline values for dronedarone, there was one exception: a larger QRS duration at the paced rhythm of 1,000 ms (Table 2). The first dose of amiodarone prolonged the CL-IVR slightly and had no direct effect on the repolarization pa-

rameters at IVR. The QT_c shortened in each animal, reaching the maximal effect at 10 min (Table 3). At the atrial level, the PP interval increased from 620 ± 180 to 785 ± 210 ms. As with dronedarone, the PP interval continued to increase, reaching a maximum at 40 min (805 ± 195 ms). The QT at 1,000 ms PCL decreased significantly after amiodarone, and the VERP increased slightly (nonsignificant); the VERP/QT ratio was increased in every dog (Table 2). As with dronedarone, no effect was observed on the QRS duration.

The second dose of amiodarone had similar effects.

Electrophysiology and proarrhythmic effects of almokalant

Before administration of almokalant, the baseline electro-physiologic characteristics were similar to the baseline values obtained at the dronedarone experiment. At the ventricular level, almokalant significantly increased the CL-IVR from 1,405 ± 260 to 1,560 ± 305 ms and all repolarization parameters (Table 4), including LV_{APD} (385 ± 55 to 505 ± 100 ms), and ΔAPD (50 ± 20 to 75 ± 40 ms). The QT time not only increased in length, but was accompanied by changes in the TU wave shape (four of seven dogs). At the atrial level, almokalant also showed a marked increase in PP interval (Table 4).

Almokalant resulted in the occurrence of TdP in five of seven dogs: four dogs showed spontaneous episodes of TdP, and in one dog, reproducible induction of TdP was obtained after PES. A representative example of a spontaneous TdP is shown in the second panel of Fig. 4.

TABLE 1. Dose-dependent electrophysiologic effects of dronedarone i.v. during IVR

	Control	Dron 10	Dron 65	Dron 2 10
CL-IVR	1,385 ± 210	1,355 ± 190	1,425 ± 255	1,495 ± 190
QT	435 ± 60	400 ± 45*	400 ± 80	360 ± 35*
QT _c	365 ± 35	340 ± 35*	335 ± 45	295 ± 35*
LV APD	395 ± 75	355 ± 55*	370 ± 60	335 ± 60*
RV APD	330 ± 45	310 ± 50	310 ± 40	300 ± 40
ΔAPD	65 ± 45	45 ± 35	55 ± 50	35 ± 35
PP	900 ± 70	575 ± 120*	585 ± 90*	615 ± 100*

Dron 10, 10 min after start of dronedarone; Dron 65, 65 min after start dronedarone at the moment the second dose is started; Dron 2 10, 10 min after start of the second dose of dronedarone; CL-IVR, cycle length of the idio-ventricular rhythm; QT, QT time; QT_c, QT corrected with the formula of Bazett; LV APD, endocardial left ventricular action-potential duration; RV APD, right ventricular APD; ΔAPD, interven-tricular dispersion = LV APD - RV APD; PP, PP interval, all values in ms to mean ± SD.

* p < 0.05 vs. control.
* p < 0.05 vs. Dron 10.

TABLE 2. Dose-dependent electrophysiologic effects of dronedarone i.v. and amiodarone i.v. during a paced rhythm of 1,000 ms

		Control	25	60	Second dose 25
		1,000	1,000	1,000	1,000
CL	DRON	110 ± 15	110 ± 15	105 ± 15	110 ± 15
	AMIO	140 ± 5 ^a	135 ± 10	135 ± 10	135 ± 5
QT	DRON	415 ± 30	390 ± 40	390 ± 40	380 ± 40
	AMIO	405 ± 25	395 ± 25 ^a	395 ± 30	385 ± 30
VERP	DRON	225 ± 30	235 ± 30	230 ± 30	230 ± 30
	AMIO	230 ± 30	235 ± 30	235 ± 30	235 ± 35
VERP/QT	DRON	0.55 ± 0.04	0.60 ± 0.04 ^a	0.60 ± 0.04	0.61 ± 0.03 ^a
	AMIO	0.56 ± 0.06	0.60 ± 0.07	0.59 ± 0.08	0.61 ± 0.09

VERP, ventricular effective refractory period; 25, 60, 25 and 60 min after the start of dronedarone; other abbreviations, see Table 1.
^ap < 0.05 vs. dronedarone.
^bp < 0.05 vs. control.

Only in the two experiments without proarrhythmic effects could the VERP be determined. In these two dogs, the VERP increased by ~15%.

Antiarrhythmic effects of dronedarone i.v.

During baseline, two dogs had ventricular repolarization disturbances, showing a long QT time and presence of deep TU waves. The ECG of one of these dogs is shown in Fig. 2B1. These ECG characteristics became more pronounced in the beats directly after the pacing trains. In one dog, PES even resulted in TdP in the absence of class III drugs. In these two dogs, dronedarone abolished these repolarization disturbances and seemed to homogenize repolarization, as shown by a marked decrease in the difference of the APD in the ventricles (ΔAPD) and disappearance of the TU wave structure (Fig. 2B2). After dronedarone, PES-induced TdP was completely prevented. Therefore, in contrast to almokalant, dronedarone administration (both dosages) did not cause any spontaneous or pacing-induced proarrhythmic activity in the form of TU-wave changes, EADs, EBs, or TdP. The antiarrhythmic effect of dronedarone was studied in more detail in four dogs with repetitive episodes of spontaneous TdP after almokalant (see Fig. 4, panel 2). In three of four dogs, PES could be performed after almokalant, and these pacing-induced

frequency changes also resulted in TdP. Dronedarone was administered 21 ± 7 min after the start of almokalant. After 2–3 min, the ectopic activity and periods of TdP started to disappear, and at 10 min (when the complete dose was injected), all the EADs and EBs were completely suppressed (see e.g., Fig. 4, panel 3). The prevention and suppression of TdP was associated with (a) a significant decrease in the QT time (525 ± 115 to 490 ± 110 ms), (b) a normalization of QT morphology (i.e., a less deep TU wave or disappearance of the biphasic TU wave (after pacing) or both), (c) shortening in the LV_{APD}, and (d) the interventricular dispersion from 110 ± 55 to 65 ± 40 ms (p < 0.05; Table 5). Again, dronedarone did not influence the CL-IVR, whereas the PP interval did increase further to 750 ms (Table 5). Repetition of PES after complete administration of dronedarone also did not lead to TdP in the presence of almokalant. The dronedarone induced decrease in QT time and LV_{APD} (both ±7–10%), and the increase in PP interval in combination with almokalant was comparable to the changes found in the seven tested dogs after the first dose of dronedarone.

Oral dronedarone

The two control electrophysiologic measurements were similar. Six hours after the first oral dose of dronedarone, a small increase in the CL-IVR and QT was

TABLE 3. Dose-dependent electrophysiologic effects of amiodarone i.v. during IVR

	Control	Amio 10	Amio 65	Amio_2 10
CL-IVR	1,430 ± 330	1,540 ± 315	1,580 ± 235	1,580 ± 260
QT	430 ± 55	430 ± 60	440 ± 70	425 ± 65
QT _c	360 ± 40	345 ± 30	350 ± 35	335 ± 35
LV APD	375 ± 65	370 ± 75	390 ± 65	375 ± 60
RV APD	320 ± 45	330 ± 45	325 ± 50	325 ± 50
ΔAPD	60 ± 35	40 ± 35	60 ± 25	50 ± 15
PP	620 ± 180	785 ± 210	760 ± 145	820 ± 145

Amio 10, 10 min after start of amiodarone; Amio 65, 65 min after amiodarone is the moment the second dose is started; Amio_2 10, 10 min after start of the second dose of dronedarone; other abbreviations, see Table 1.

TABLE 4. Electrophysiologic effects of almokalant i.v.

	Control	Almokalant 10
CL-IVR	1,405 ± 340	1,560 ± 305 ^a
QT	410 ± 60	510 ± 115 ^a
QT _c	350 ± 25	410 ± 70 ^a
LV APD	385 ± 55	505 ± 100 ^a
RV APD	335 ± 45	430 ± 95 ^a
ΔAPD	50 ± 20	75 ± 40 ^a
PP	530 ± 20	595 ± 45 ^a

Almokalant 10, 10 min after the start of almokalant; other abbreviations, see Table 1.
^ap < 0.05 vs. control.

31

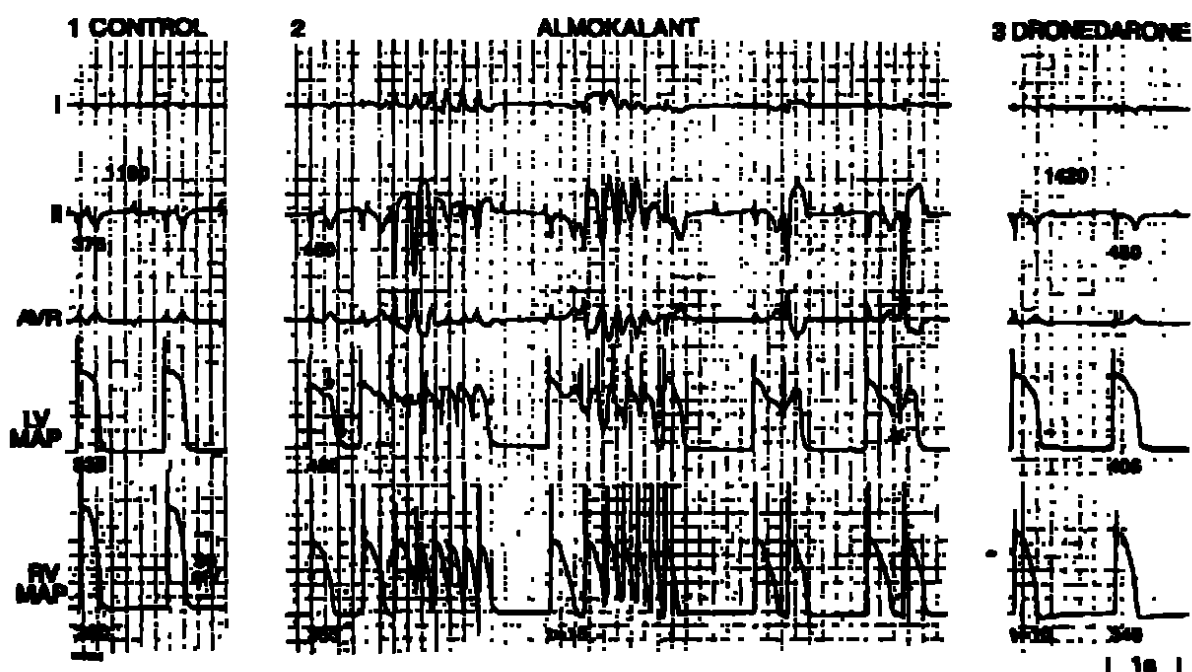


FIG. 4. Effect of dronedarone on almokalant-induced torsade de pointes (TdP). This figure consists of three panels with the same configuration as in Fig. 2. In panel 1, the baseline situation is shown with smooth AP morphology and an interval of 48 ms (336–280 ms). After almokalant (0.12 mg/kg/10 min), the repolarization changes, as evidenced by an increase in QT time, APD, and interval of dispersion (ΔAPD). Early afterdepolarizations (EADs) occur as indicated by the arrows (panel 2), and we see two short episodes of TdP, in the presence of triggered EADs (asterisk) and an interval of dispersion of 480 ms (LVAPD) – 355 ms (RVAPD) = 125 ms. Fifteen minutes after almokalant, dronedarone (2.5 mg/kg/10 min) is started. At the end of the dronedarone infusion (panel 3), repolarization is diminished (e.g., the LVAPD is 405 ms, and the ΔAPD has halved from 125 to 65 ms). This decrease is accompanied by the suppression of TdP episodes, ectopic beats, and EADs.

observed (Fig. 5). The increase in QT_c reached significance at 21 days (275 ± 15 to 305 ± 10 ms; $p < 0.05$).

DISCUSSION

In this study, we evaluated the short-term electrophysiologic effects of dronedarone, i.v., and related them to the occurrence and suppression of ventricular repolarization abnormalities and acquired TdP arrhythmias. Like amiodarone, dronedarone lacked an acute class III effect in dogs with CAVB. Dronedarone even shortened repolarization, resulting in the prevention and suppression of almokalant-induced TdP.

TABLE 5. Electrophysiologic effects of dronedarone i.v. after almokalant-induced TdP

	Control	Almokalant 21 ^a	Dron 10
CL-IVR	1,380 ± 400	1,535 ± 355 ^b	1,535 ± 320
QT	365 ± 55	525 ± 115 ^b	490 ± 110 ^c
LV APD	380 ± 45	505 ± 110 ^b	455 ± 80 ^c
RV APD	320 ± 50	390 ± 65 ^b	385 ± 60
ΔAPD	55 ± 10	110 ± 55	65 ± 40 ^c
FP	580 ± 125	660 ± 175	750 ± 175 ^c
TdP	0/4	4/4 ^b	0/4 ^c

^a Starting point of dronedarone at 21 ± 7 min after almokalant; abbreviations similar to Table 1.

^b $p < 0.05$ vs. control.

^c $p < 0.05$ vs. almokalant.

Animal model of acquired torsade de pointes arrhythmias

To examine the short-term, dose-dependent effects of dronedarone on different ventricular repolarization parameters and repolarization-related arrhythmias, we decided to use the CAVB dog for three reasons: (a) separation between atrial activity and ventricular rhythm; (b) presence of nonuniform repolarization, favoring arrhythmogenesis; and (c) high susceptibility to TdP arrhythmias after class III drugs. In this model, the bradycardia-induced volume overload leads to biventricular hypertrophy and electrical remodeling (33); besides the anticipated lengthening in ventricular repolarization, we described the appearance of another important proarrhythmic variable, interventricular dispersion. The ΔAPD (a) is bradycardia dependent; (b) at CAVB, further increased by the administration of class III agents (e.g., almokalant; 27,29); and (c) promotes the emergence of EAD-dependent acquired TdP (27,29).

Almokalant, a pure I_{Kr} blocker, has shown a proarrhythmic effect in ~4% of the patients (34) and has been withdrawn from further clinical trials. After almokalant, repolarization disturbances were clearly visible in almost all dogs. In addition, EADs occurred in both ventricles, followed in time by (triggered) EBs and the spontaneous occurrence of multiple runs of TdP (Fig. 4). In those dogs showing spontaneous TdP, PES also resulted in the induction of TdP, which is reproducible not

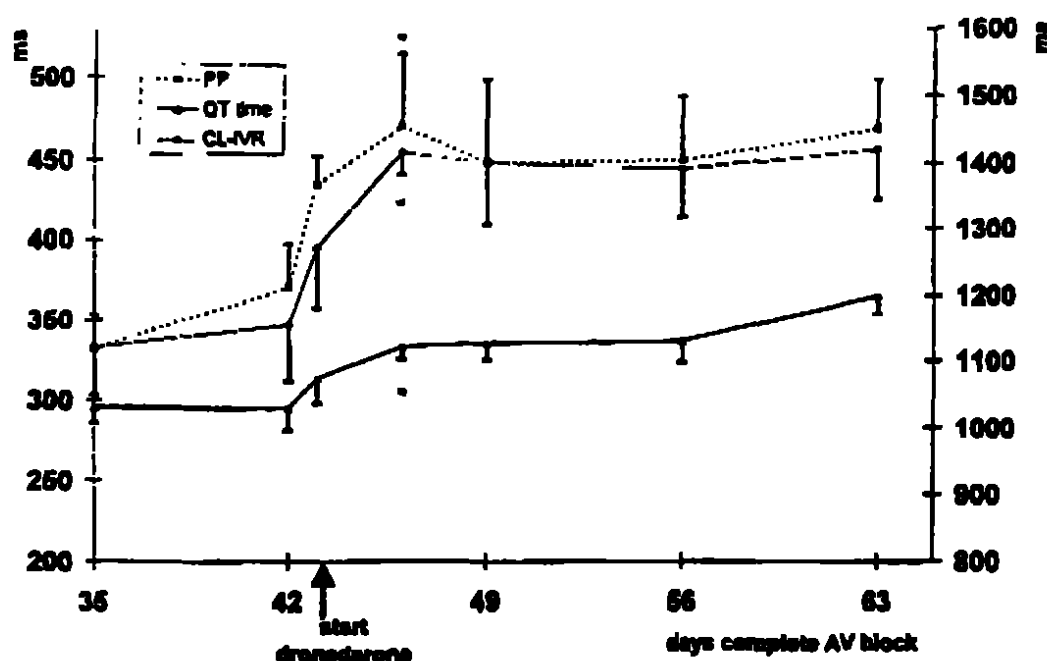


FIG. 5. Effect of oral dronedarone (20 mg/kg twice daily) on electrophysiologic parameters during idioventricular rhythm. The average values ($\pm$ SEM) of the CL-IVR, QT time, and PP interval are depicted at the Y axis as a function of time after the start of oral dronedarone (X axis). The two control measurements performed at day 35 and 42 after creation of CAVB had similar results. Six hours after the first oral dose of dronedarone (day 43), the parameters increased, reaching significance at day 47 ($p < 0.05$ vs. control).

only within one experiment but also during subsequent experiments (26).

The induction of TdP by pacing is sometimes possible during baseline circumstances in animals demonstrating severe ventricular repolarization abnormalities on the ECG in the form of TU waves (postpacing). Prevention and suppression of TdP by pacing or drugs (26,27) is associated with an inhibition of the EADs and a shortening of the Δ APD.

Electrophysiologic effects of dronedarone i.v. and amiodarone i.v.

In anesthetized dogs with CAVB, the administration of dronedarone i.v. did not result (<60–120 min) in short-term class III effects. On the contrary, we noticed a dose-dependent shortening of ventricular repolarization without influencing the CL-IVR in our dogs. Intravenous amiodarone-treated dogs exhibited a similar trend with a similar QT interval, whereas the CL-IVR increased.

Dronedarone, i.v., showed a different temporal effect on repolarization as on PP interval. The maximal shortening of the repolarization was reached at 10 min, whereas the PP interval showed a further increase with a maximum at 40 min (Fig. 3).

This is for the first time that a decrease in QT time was described for an amiodarone-related compound. In the literature, similar or increased values in QT time were reported, most probably related to the significant increased interval (pronounced bradycardia) described in the other studies (23,24). When the dogs would have been in normal conducted sinus rhythm, the slowed PP rate could

have increased the QT more than the actual decrease now observed by dronedarone.

Another possible important finding is the increased VERP/QT ratio, which is based on the unchanged or small increase in VERP accompanied by the reported shortening of QT time. This will lead to postrepolarization refractoriness, a finding some authors considered an important antiarrhythmic property (35). The VERP/QT ratio was determined during a steady-state pacing at a CL of 1,000 ms.

Dronedarone showed dose-dependent electrophysiologic changes in QT and PP interval (Table I, Fig. 3).

In the literature, several short-term electrophysiologic studies were published of drugs with amiodarone-like structures without the iodine content. These drugs (e.g., butoprozine (L 9394) and prifuroline) also decreased heart rate (PP interval) in dogs. However, butoprozine (36) had no effect on QT, APD, and VERP, and prifuroline (37) increased the VERP mainly based on a Na^+ blockade, as evidenced by an increase in QRS duration.

Antiarrhythmic effects of dronedarone, i.v.

In many screening models of arrhythmias (24,38,39), dronedarone, i.v., was shown to have antiarrhythmic effects similar to those of amiodarone, but at lower dosages. These antiarrhythmic effects were associated with the induced bradycardia or the increased VERP or both (24).

Our first impression that dronedarone might have an effect on repolarization-dependent arrhythmias came

from the disappearance of the TU waves in the dogs receiving the drug for the electrophysiologic study. This was an unexpected finding, which we normally refer to as homogenization of repolarization, because it is accompanied by shortening in QT time and Δ APD (27,40). Therefore, we investigated whether dronedarone, i.v., could prevent or suppress or both the spontaneous or pacing-induced TdP seen after almokalant. This was clearly the case. Within minutes after administration of dronedarone, TdP became suppressed, just as did the EBs and the EADs.

Because there are no data on the antiarrhythmic effects of dronedarone in repolarization-related arrhythmias, we can refer to amiodarone only for comparative purposes. Antiarrhythmic effects of amiodarone, i.v., in patients with TdP have been described (19,20). Rankin et al. (20) reported that the prevention of TdP with i.v. amiodarone was associated with an increase in QT time, possibly related to the slowing in heart rate after amiodarone. They suggested that the prevention of TdP could be due to (a) the suppression of the EBs (EADs) preceding the TdP, or (b) a homogenization of the APD throughout the heart, or both. This corresponds with our observation of the decrease in Δ APD and suppression of EADs by dronedarone, i.v..

Possible ionic background responsible for the observed changes

Changes in electrophysiologic parameters can be the result of effects on different ionic currents. An extensive review on the complex cellular electropharmacology of amiodarone can be found in reference 4). From our and other *in vivo* studies (23–25), we may assume similar short-term effects of dronedarone and amiodarone, although reached with another dosage.

The observed decrease in repolarization time can be explained by a relatively larger block of inward currents (Ca^{2+} or Na^{+} blockade or both) than outward currents (K^{+} blockade), resulting in a shortened APD (42). These actions could also be responsible for the change in VERP/QT. During the plateau phase of the AP, a small block of Na^{+} currents may lead to a shortening of APD, as illustrated by the electrophysiologic effects of quinidine (43).

The bradycardic effect on sinus level can in principle be reached by (a) the β -blocking activity (25), (b) the Ca_v channel blockade, or (c) the potassium channel blocking effect, as seen with pure class III drugs, which cause an increase in both PP interval and the CL-IVR, or a combination of these (Table 4; 26,29). In view of our results, the latter possibility seems not likely for dronedarone.

The suppression of EADs and prevention of TdP could be due to Ca^{2+} blockade and also Na^{+} blockade (44). In addition, a possible role of α -adrenergic blockade (24) should be mentioned because α -adrenergic stimulation has been shown to play a role in the genesis of acquired TdP arrhythmias in the rabbit model (45).

Long-term electrophysiologic effects of oral dronedarone

In contrast to the short-term administration oral dronedarone increases both the PP interval and the CL-IVR and caused a significant increase in repolarization, which at day 21 was independent of CL. Long-term amiodarone in humans also leads to a slowing of the heart rate and an increased repolarization (13,15).

Can dronedarone replace amiodarone?

Amiodarone has been established as one of the most effective antiarrhythmic agents currently available for clinical use (1,2,6–12). The results of these large-scale clinical trials are in large contrast to the detrimental effects reported with class I (3,4) and pure class III agents (5). The exact pharmacologic mechanism responsible for amiodarone's activity is still not clear but goes beyond its reported class I and III activity. It could be based on additional class II (both α - and β -antiadrenergic action) or class IV action or both. Moreover, an interaction with the thyroid receptor cannot be excluded.

Dronedarone, i.v., has a similar mode of action (i.e., Ca^{2+} , Na^{+} , and noncompetitive adrenergic blockade), occurring at even lower dosages (23–25). The oral use of dronedarone also slows the heart rate. In addition, this compound might lack (part of) the feared side effects because of the absence of iodine. Side effects like pulmonary toxicity and thyroid dysfunction (21,22) after oral use are considered the main restriction in the use of amiodarone and a major reason for discontinuation (2,21,22) of amiodarone therapy in 40% of the patients (2,39).

The protection against repolarization disturbances and repolarization-related arrhythmias (TdP) by dronedarone combined with an increased VERP/QT ratio may result in a powerful antiarrhythmic agent.

Limitations

In this study, we used dogs with CAVB to study the electrophysiologic effects of dronedarone. In contrast to data reported in sinus rhythm dogs, the CL-IVR does not alter after dronedarone, i.v.. This could have influenced part of the results, especially because of the temporal difference between repolarization and PP interval. On the other hand, it gives a good idea of the direct effect of dronedarone on ventricular repolarization. Also, we did not investigate the frequency-dependent electrophysiologic effects of dronedarone, although the (relative) effects observed at CL-IVR ($\pm 1,400$ ms) and 1,000 m were similar.

Comparison of oral and i.v. dronedarone might be confounded by the fact that dronedarone, i.v., was administered while the dogs were under (halothane) anesthesia, whereas the oral dronedarone was studied awake. A possible contribution of halothane to the observed effects of dronedarone is conceivable.

Dronedarone was dissolved in a mixture of saline and PEG 400. We did not examine the electrophysiologic effects of the solvent mixture itself. Because PEG 400 h

been reported to prolong the QT time (23), it is not very likely that the solvent is a major determinant of the described electrophysiologic effects in this study (a shortening of repolarization).

CONCLUSION

Dronedaron, i.v., does not have a class III action in dogs with CAVB. It shortens ventricular-repolarization parameters, resulting in suppression of EAD-dependent acquired TdP. The increased VERP/QT ratio after dronedarone may indicate an important second antiarrhythmic property.

Acknowledgment: This study was financially supported by a grant of the Dutch Heart Foundation (94.010) and by Sanofi Recherche (Montpellier, France). We also thank ASTRA Sweden for providing almokalant and the Medtronic Bakken Research Center for the epicardial electrodes.

REFERENCES

1. Nattel S, Singh BN. Comparative mechanisms of action of antiarrhythmic drugs. In: Singh BN, Wellens HJJ, Hirakawa M, eds. *Electropharmacological control of cardiac arrhythmias*. Mount Kisco, New York: Futura Publishing, 1994:207-24.
2. Connolly SJ. Effect of prophylactic amiodarone on mortality after acute myocardial infarction and in congestive heart failure: meta-analysis of individual data from 6500 patients in randomized trials: amiodarone trials meta-analysis investigators. *Lancet* 1997;350:1417-24.
3. CAST investigators. Mortality and morbidity in patients receiving encainide, flecainide and placebo: the Cardiac Arrhythmia Suppression Trial. *N Engl J Med* 1991;324:781-8.
4. ESVEM investigators. The ESVEM trial: electrophysiological study versus electrocardiographic monitoring for selection of antiarrhythmic therapy of ventricular tachyarrhythmias. *Circulation* 1989;79:1354-60.
5. White AL, Camm AJ, de Royer de H, et al. The SWORD investigators: effect of β -totolet on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. *Lancet* 1996;348:7-12.
6. Jellin DG, Camm AJ, Janse MJ, Schwartz PJ, Simon P. Randomized trial of effect of amiodarone on mortality in patients with left ventricular dysfunction after recent myocardial infarction: ENIAT. *Lancet* 1997;349:867-74.
7. Calais JA, Connolly SJ, Roberts R, Goss M. Randomized trial of outcome after myocardial infarction in patients with frequent or repetitive ventricular premature depolarizations: CAMIAT. *Lancet* 1997;349:875-82.
8. Greene HL. Randomized antiarrhythmic drug therapy in survivors of cardiac arrest (the CASCADE study): CASCADE investigators. *Am J Cardiol* 1993;72:220-7.
9. Deval HC, Nal DR, Graciani HO, Perone SV, Borron GR, Curiel R. Randomized trial of low dose amiodarone in severe congestive heart failure (GESICA). *Lancet* 1994;344:493-8.
10. Mason BM, Fisher SG, Doodwanla PC, Singh BN, Flecher RD, Singh BN. Effect of amiodarone on clinical status and left ventricular function in patients with congestive heart failure: CHF STAT investigators. *Circulation* 1996;93:2128-34.
11. Kowey PR, Lavine JH, Harte JM, et al. Randomized double blind comparison of intravenous amiodarone and bretylium in the treatment of patients with recurrent hemodynamically destabilizing ventricular tachycardia or ventricular fibrillation. *Circulation* 1995;92:3253-63.
12. Schelenman MM, Lavine JH, Cannon DS, et al. Dose ranging study of intravenous amiodarone with life threatening ventricular tachyarrhythmias. *Circulation* 1995;92:3264-72.
13. Wellens HJJ, Brugada P, Abdullah H, Dassen WR. A comparison of the electrophysiological effects of intravenous and oral amiodarone in the same patient. *Circulation* 1984;69:120-4.
14. Kowey PR, Marinchuk RA, Riah SJ, Pillart PA. Intravenous amiodarone. *J Am Coll Cardiol* 1997;29:1190-8.
15. Mitchell LB, Wyse G, Gillis AM, Duff HJ. Electropharmacology of amiodarone therapy initiation: time courses of onset of electrophysiologic and antiarrhythmic effects. *Circulation* 1989;80:34-42.
16. Holmlow SH, Singh BN. Proarrhythmia with class III antiarrhythmic drugs: definition, electrophysiologic mechanisms, incidence, predisposing factors, and clinical implications. *J Cardiovasc Electrophysiol* 1995;6:920-36.
17. Hii JTY, Wyse DG, Gillis AM, Duff HJ, Solyto MA, Mitchell LB. Premordial QT time (interval) dispersion as a marker of torsade de pointes: disparate effects of class IA antiarrhythmic drugs and amiodarone. *Circulation* 1992;86:1376-82.
18. Nguyen TP, Schelenman MM, Sagar J. Polymorphic ventricular tachycardia: clinical characterization, therapy and QT interval. *Circulation* 1986;74:240-9.
19. Manton TA, Zhenia TA, Serminato JJ, Parker M, Lasch M, Kebou RF. Amiodarone in patients with previous drug mediated torsade de pointes: long term efficacy. *Ann Intern Med* 1989;111:574-80.
20. Rankin AC, Pringle SD, Colthe SM. Acute treatment of torsades de pointes with amiodarone: proarrhythmic and antiarrhythmic association of QT prolongation. *Am Heart J* 1990;119:185-6.
21. Singh BN. Antiarrhythmic actions of amiodarone: a profile of a paradoxical agent. *Am J Cardiol* 1996;78(suppl 4A):41-53.
22. Harris L, Roussel R, eds. *Amiodarone: pharmacology, pharmacokinetics, neurology, clinical effects*. Paris: Medici Paris, 1984.
23. Manning A, Thiesse V, Hodge D, Richard J, Heyndrickx JP, Chantelois P. SR 33589, a new amiodarone-like antiarrhythmic agent: electrophysiological effects in anesthetized dogs. *J Cardiovasc Pharmacol* 1993;25:252-61.
24. Fumero O, Manning A, Chantelois P. Effects of a new amiodarone like agent, SR 33589, in comparison to amiodarone, β -totolet, and lignocaine, on isoproterenol-induced ventricular arrhythmias in anesthetized pigs. *J Cardiovasc Pharmacol* 1993;26:570-6.
25. Hodge D, Heyndrickx JP, Chantelois P, Manning A. SR 33589: a new amiodarone-like antiarrhythmic agent: anti-adrenergic activity in anesthetized and conscious dogs. *Eur J Pharmacol* 1993;279:25-32.
26. Vos MA, Verdruyn SC, Gorgels APM, Lipson GC, Wellens HJJ. Reproducible induction of early afterdepolarizations and torsade de pointes arrhythmias by β -totolet and pacing in the dog with chronic sino-ventricular block. *Circulation* 1993;88:570-72.
27. Verdruyn SC, Vos MA, Zande van der J, van der Hout FF, Wellens HJJ. Role of inter-ventricular dispersion of repolarization in acquired torsade de pointes arrhythmias: reversal by magnesium. *Cardiovasc Res* 1997;34:353-63.
28. Vos MA, Gorgels APM, Lipson GC, de Groot SHM, Lousissen HDM, Wellens HJJ. Mechanism specific anti-arrhythmic effects of the potassium channel activator levcromakalim against repolarization dependent tachycardias. *J Cardiovasc Electrophysiol* 1994;5:731-42.
29. Verdruyn SC, Vos MA, Zande van der J, Kalcar A, Wellens HJJ. Further observations to confirm the importance of dispersion of repolarization and early afterdepolarizations in the genesis of acquired torsade de pointes arrhythmias: comparison between almokalant and β -totolet using the dog as its own control. *J Am Coll Cardiol* 1997;30:1575-84.
30. Loerens HM, Vos MA, Duff den K, Zande van der J, Wellens HJJ. Is the ventricular effective refractory period different when determined by incremental versus decremental scanning?: the effect of pacing cycle length, β -totolet, and levcromakalim. *Pacing Clin Electrophysiol* 1994;17:2084-9.
31. Vaidin S, Heller K, Barron HV, et al. Post extrasystolic U wave augmentation: a new marker of increased arrhythmic risk in patients without the long QT syndrome. *J Am Coll Cardiol* 1996;28:1744-52.
32. Winer BJ. *Statistical principles in experimental design*. 2nd ed. New York: McGraw-Hill, 1977.

52
49

33. Vos MA, Groot de SHMA, Verduyn SC, et al. Enhanced susceptibility for acquired torsade de pointes arrhythmias in the dog with chronic complete atrioventricular block is related to cardiac hypertrophy and electrical remodeling. *Circulation* 1998;98:1125-35.
34. Svernhage E. Torsades de pointes (TdP) during treatment with sotalolol [Abstract]. *Eur J Cardiac Pacing Electrophysiol* 1994; 4(suppl 4):216.
35. Franz MR, Cozzard A. Frequency dependent effects of quinidine on the relationship between action potential duration and refractoriness in situ. *Circulation* 1988;77:1174-84.
36. Sassié A, Fajuri A, Hirsch JL, de CM, Masse C, Poëch P. Electrophysiological properties of bepridone studied by multiple intracardiac recordings on the anesthetized dog. *Arch Int Pharmacodyn Ther* 1983;261:249-59.
37. Jallion P, Hackle J, Jais JM, Poveda SJ, Cheymol G. Acute effects of intravenous priflutelone and amiodarone on canine cardiac automaticity, conduction, and refractoriness. *J Cardiovasc Pharmacol* 1992;4:486-92.
38. Hodrige D, Chatelet M, Manning M. SR 33589—effect on atrial fibrillation in dogs compared with amiodarone. In: Hausen S, Kjeldsen K, eds. *International society for heart research European section meeting*. Copenhagen: Bologna Mondazzi Editore, 1994: 681-4.
39. Sanofi Recherche. *Clinical investigator's brochure SR33589*. Jans 1997.
40. Opstal van JM, Verduyn SC, Vos MA, van der Zande J, Wellens HJJ. Homogenization of ventricular repolarization is responsible for suppression of torsade de pointes arrhythmias in dogs [Abstract]. *Eur Heart J* 1996;17(suppl):417.
41. Kodama I, Kameya K, Toyama J. Cellular electropharmacology of amiodarone. *Cardiovasc Res* 1997;35:13-29.
42. Gaudier P, Marion A, Bertrand JP, Tournaud Y, Nisato D. Electrophysiological characterization of dronedarone (SR 33589): a new amiodarone like agent, in cardiac ventricular myocytes [Abstract]. *Eur Heart J* 1997;18:269.
43. Sotnikov EA, Anyukhovsky EP, Razon MR. Effects of quinidine on repolarization in canine epicardium, midmyocardium, and endocardium: I. in vitro study. *Circulation* 1997;96:4011-8.
44. Chezalviel GF, Davy JM, Polier JM, Weissburger J. Mexiletine antagonizes effects of sotalol on QT interval duration and its proarrhythmic effects in a canine model of torsade de pointes. *J Am Coll Cardiol* 1995;26:787-92.
45. Carlsson L, Almgren O, Duker G. QTU-prolongation and torsades de pointes induced by putative class III antiarrhythmic agents in the rabbit: ecology and interventions. *J Cardiovasc Pharmacol* 1990;16:276-83.
46. Chezalviel GF, Davy JM, Polier JM, Weissburger J. Mexiletine antagonizes effects of sotalol on QT interval duration and its proarrhythmic effects in a canine model of torsade de pointes. *J Am Coll Cardiol* 1995;26:787-92.
47. Carlsson L, Almgren O, Duker G. QTU-prolongation and torsades de pointes induced by putative class III antiarrhythmic agents in the rabbit: ecology and interventions. *J Cardiovasc Pharmacol* 1990;16:276-83.

3

RAPPORT DE RECHERCHE

P.D. 1995

p. 252-261

10

Journal of Cardiovascular Pharmacology
35:25-361 © 1993 Raven Press, Ltd., New York

XP-001024497

SR 33589, a New Amiodarone-like Antiarrhythmic Agent: Electrophysiological Effects in Anesthetized Dogs

Allan Manning, Vincent Thisse, Dominique Hodeige, Jean Richard, Jean Pierre Heyndrickx, and Pierre Chatelain

Department of Pharmacology, Sanofi Research Centre, Sanofi Pharma, Brussels, Belgium

Summary: We compared the electrophysiological effects of a new amiodarone-like agent, SR 33589, with those of amiodarone. Mongrel dogs were anesthetized with chloralose, and electrodes were implanted in right atrium and ventricle for electrical stimulation and regional ECG measurement. Sinus cycle length (CL), AH interval, Wenckebach CL (WCL), atrial, atrioventricular node, and ventricular effective refractory periods (AERP, AVNERP, VERP), and parameters calculated from surface ECG were measured. SR 33589 was administered intravenously (i.v.) at 1, 2.5, or 5 mg/kg followed 60 min later by a second similar dose. The same protocol was followed with amiodarone 5 mg/kg, which reduced heart rate (HR) by 19% ($p < 0.05$), increased WCL by 31% ($p < 0.01$), AH interval by 14% ($p < 0.05$) and AERP, AVNERP, and VERP by 13% ($p < 0.05$), 19% ($p < 0.05$), and 11% ($p < 0.01$) respectively. No effect was observed on HV or PQ

intervals. A second administration of 5 mg/kg changed these indexes further. SR 33589 (2.5 mg/kg) reduced CL by 21% ($p < 0.001$), increased WCL by 44% ($p < 0.001$), AH interval by 24% ($p < 0.01$), and AERP, AVNERP, and VERP by 17% ($p < 0.001$), 63% ($p < 0.01$), and 11% ($p < 0.01$) respectively, with an 18% increase in PQ interval ($p < 0.05$) but no significant effect on HV interval. Higher doses (5 mg/kg) and/or administration of a second dose both resulted in greater changes. Both amiodarone and SR 33589 prolonged VERP more at longer CL than shorter CL, but the degree of reduction at shorter CL was less with SR 33589 than with amiodarone. Results suggest that acute administration of SR 33589 results in electrophysiological actions similar to those produced by amiodarone. **Key Words:** SR 33589—Amiodarone—Electrophysiology—Electrocardiogram.

Amiodarone is one of the most effective antiarrhythmic agents currently available for clinical use for suppression of atrial fibrillation and life-threatening ventricular arrhythmias (1-3). However, the exact pharmacologic mechanisms responsible for this action have not been clearly defined. Amiodarone possesses an array of potential antiarrhythmic actions that all may play a role in its clinical efficacy. These include potential antisympathetic activity (4,5), prolongation of ventricular action potential duration (APD) and effective refractory periods (ERP) (6,7) and inhibition of the fast sodium channel (8,9), slow calcium channel (10,11), and various potassium channels (12,13). Certain unwanted pharmacologic actions may restrict clinical usage of amiodarone, however, including potential pulmonary toxicity (14,15) and an

interaction with thyroid function believed to be due to the presence of iodine substituents on the amiodarone molecule (2).

SR 33589 is a benzofuran derivative structurally related to amiodarone (Fig. 1) that was recently shown to possess significant antiarrhythmic actions similar to and possibly more potent than those of amiodarone (16,17). We compared the acute electrophysiological actions of SR 33589 after its intravenous (i.v.) administration in anesthetized dogs with those of amiodarone.

METHODS

Electrophysiological actions at basal heart rate (18). *Surgical techniques.* Mongrel dogs (weighing ~10 kg) of either sex were used. Animals were an-

Received January 10, 1994; revision accepted September 23, 1994.

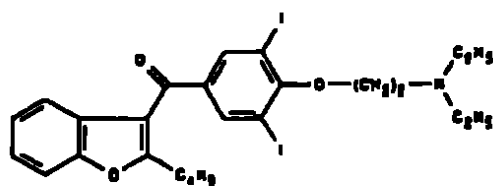
Address correspondence and reprint requests to Dr. A. S.

Manning at Sanofi Winthrop Ltd., 1 Onslow St., Guildford, Surrey GU1 4YS, England.

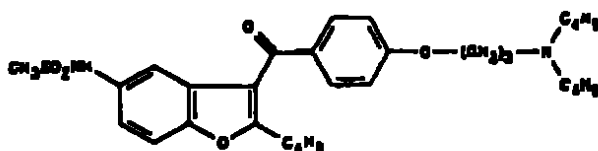
36

ELECTROPHYSIOLOGICAL ACTIONS OF SR 33589

253



AMIODARONE



SR 33589

FIG. 1. Structures of SR 33589 and amiodarone.

thetized with 0.8% α -chloralose (80 mg/kg i.v.) and ventilated with air by a Bird M.8 ventilator (flow rate equivalent to 12 cycles/min). Four electrodes were positioned (one attached to each limb) to obtain a surface ECG recorded from lead II. Using fluoroscopic monitoring, we inserted two intracardiac electrodes through the jugular vein and positioned them in right atrium; one was used for stimulation of the sinoatrial (SA) node and the second was used to monitor the atrial electrogram. Two additional intracardiac electrodes were positioned through the femoral vein in the right ventricle, one to stimulate the apex and the second to monitor His bundle potential. These catheters were connected to a programmable stimulator or amplifiers and a physiograph recorder (Siemens) to monitor and record the various ECGs.

Parameters monitored. The following indexes of cardiac electrophysiological function were monitored: sinus cycle length (SCL); AH interval (as a measure of intranodal conduction time); HV interval (as a measure of conduction time in the His-Purkinje system); a range of parameters calculated from the surface ECG, including PQ, QRS, QT, and QTc intervals, calculated according to the method of Bazett (18); and refractory periods (atrial, atrioventricular node, and ventricular: AERP, AVNERP, VERP) calculated by atrial or ventricular-coupled stimulation with a programmable electronic stimulator (Janssen ISI-SU2) with rectangular current pulses (2-ms duration at twice diastolic threshold). Programmed single premature atrial or ventricular stimuli were delivered after fixed-rate pacing at a 400-ms CL. The coupling interval of the premature stimuli was reduced by 10 ms after a train of eight beats until no response was recorded. Wenckebach CL (WCL) was calculated by increasing the rate of stimulation of the SA node until no ventricular depolarization was observed.

Drug administration. Amiodarone 5 mg/kg was administered as a 5% solution in distilled water. SR 33589 was administered as a 1% solution in distilled water at 1 mg/kg, 2% solution in distilled water at 2.5 mg/kg, and as a 1% polyethylene glycol (PEG) solution with distilled water (2:1) at the highest dose of 5 mg/kg. In each case, 5 mg/kg amiodarone or 1, 2.5 or 5 mg/kg SR 33589 was administered i.v. in 2 ml, followed by a second similar dose 60 min later. Immediately after injection, the surface ECG and the His bundle and atrial ECGs were recorded and intervals were measured every minute for the first 10 min. The same intervals were then measured every 10 min. ERPs and WCL were calculated at 10 and 50 min after administration of the first dose and at 10, 50, and 90 min after administration of the second dose. Isotonic NaCl 4 ml was administered to a control group of 5 dogs according to the same protocol. Each other group contained 6 dogs.

Frequency-dependent effects of amiodarone and SR 33589

Surgical techniques. Mongrel dogs weighing ~10 kg of either sex were used. The surgical techniques used were essentially the same as those used in the first study in which electrodes were positioned on each limb of the anesthetized animals to obtain a surface ECG. However, only one electrode was inserted through the femoral vein and positioned at the apex of the right ventricle. This electrode was connected to a programmable stimulator connected to a physiograph for stimulation of the ventricle and recording of the ventricular signal.

Parameters measured. The effects of amiodarone and SR 33589 on VERP were measured at drive CL ranging from 400 to 200 ms in increments of 40 ms. VERP was measured as described in the previous section. Ventricular refractoriness was defined as the response of the ventricle to the introduction of premature stimuli after a sequence of eight beats, and ERP was defined as the longest coupling interval between the basic drive CL and the first premature stimulus that failed to evoke a ventricular response. EPP was measured at 20, 50, and 80 min after drug administration.

Drug administration. Drugs were dissolved and administered as described previously. All groups consisted of 6 dogs. Groups received either a vehicle solution, 2.5 mg/kg i.v. SR 33589, or 5 mg/kg i.v. amiodarone.

Statistics

Results were analyzed statistically by Student's *t* test for paired variables. Differences between mean values were considered significant at $p < 0.05$. Comparisons were made in only one direction, between mean values observed at a certain time after drug administration and mean values measured before drug administration (time 0).

RESULTS

Graphic representation of electrophysiological activity

To aid comparison and visualization of the electrophysiological activity we transferred the six parameters (SCL, AH interval, WCL, AERP, AVNERP, and VERP) onto a star symbol, with the six equal branches around a central hexagon used to

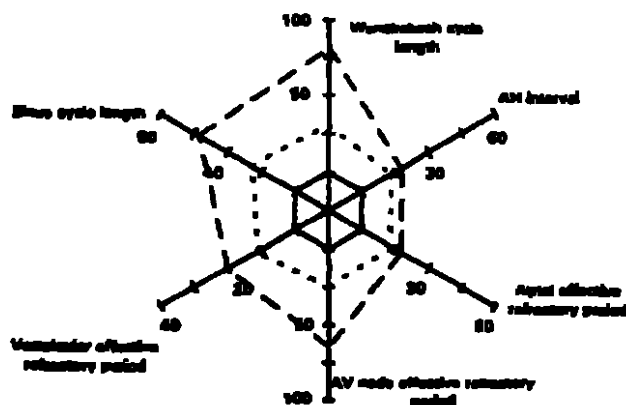
89
51

FIG. 2. Electrophysiological changes observed after administration of 5 (....) + 5 mg/kg amiodarone 80 min later (—) intravenously.

indicate 0 variation (Figs. 2–5). Mean values of effects during administration of the first dose were calculated and superimposed on the star symbol. Similarly, mean values of the effects of amiodarone and SR 33589 after administration of the second dose were calculated and also superimposed on the star symbol.

Electrophysiological effects of amiodarone

The electrophysiological effects of amiodarone are shown in Tables 1 and 2 and Fig. 2.

Effect on SCL. No significant changes were observed in the vehicle-treated group. A maximal, nonsignificant increase in SCL was noted 40 min after the first injection so that SCL was prolonged by 13% [from 443 ± 46 to 500 ± 32 ms, NS; i.e., a reduction in heart rate (HR) of -14% from 141 ± 14 to 122 ± 8 beats/min, NS] and 70 min after the second injection so that SCL was increased by 25% (from 443 ± 46 to 553 ± 74 ms, NS; i.e., a reduction in HR of -19% from 141 ± 14 to 115 ± 12 beats/min, NS).

Administration of amiodarone caused a slight, nonsignificant shortening of SCL immediately after administration of both doses: by 5% from 501 ± 26

to 474 ± 25 ms and by 7% from 624 ± 43 to 580 ± 45 ms. After initial shortening administration of first dose of amiodarone caused progressive prolongation of SCL; maximal but nonsignificant change was observed after 50 min when SCL was increased by 26% (from 501 ± 26 to 632 ± 46 ms, NS), equivalent to a reduction in HR of 19% (from 121 ± 6 to 98 ± 8 beats/min, $p < 0.05$). A second administration of 5 mg/kg amiodarone further increased SCL after 70 min SCL was prolonged by 61%: from 501 ± 26 to 807 ± 83 ms, $p < 0.05$, equivalent to reduction in HR of 35%, from 121 ± 6 to 78 ± 10 beats/min, $p < 0.05$.

Effect on AH interval. In the vehicle-treated group, AH interval was stable throughout the study. Amiodarone 5 mg/kg prolonged the AH interval significantly. A maximal increase was noted after 8 min, when the interval was prolonged 14% (from 85 ± 6 to 96 ± 8 ms, $p < 0.05$). Administration of the second dose of amiodarone induced slightly greater prolongation of the AH interval; after 50 min, it was prolonged by 18% (from 85 ± 6 to 100 ± 5 ms, $p < 0.05$).

Effect on HV interval. In the vehicle-treated group, the HV interval was stable throughout the study. Administration of amiodarone 5 mg/kg prolonged HV interval progressively but nonsignificantly; at the end of the first observation period it was increased by 13% (from 19 ± 2 to 22 ± 2 ms, NS). The second dose of amiodarone induced slightly greater, but still nonsignificant prolongation of the HV interval; at the end of the experimental protocol, it was prolonged by 17% (from 19 ± 2 to 23 ± 3 ms, NS).

Effect on PQ, QRS, and QTc intervals. No significant change was noted in PQ interval in the vehicle-treated group or in the group treated with amiodarone. In the vehicle-treated group, the QRS complex was slightly (maximum variation 7%), significantly ($p < 0.05$) prolonged during the experimental observation period (from 33.8 ± 2 to 36.2 ± 1 ms). Amiodarone 5 mg/kg induced a similar or longer prolongation of the QRS complex (max

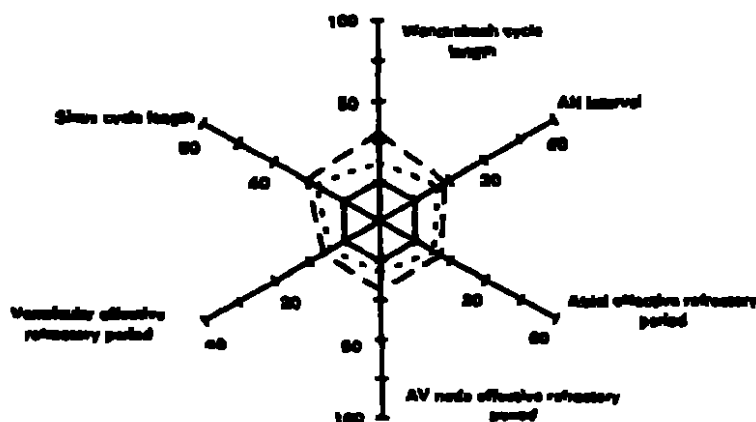


FIG. 3. Electrophysiological changes observed after administration of 1 + 1 mg/kg SR 335 intravenously. Results presented as in Fig. 2.

40

ELECTROPHYSIOLOGICAL ACTIONS OF SR 33589

255

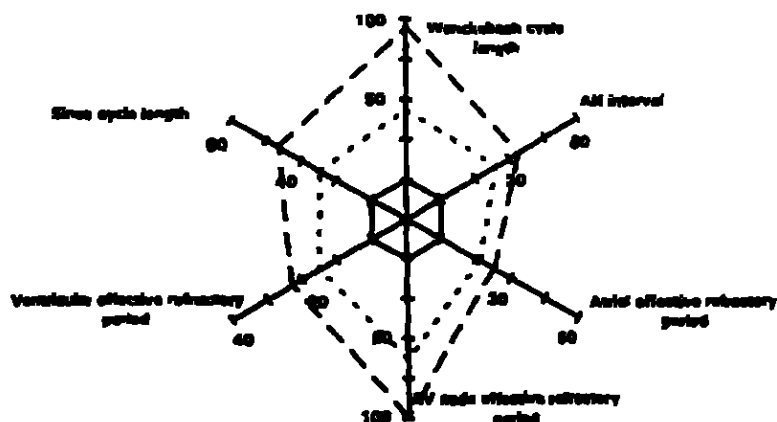


FIG. 4. Electrophysiological changes observed after administration of 2.5 + 2.5 mg/kg SR 33589 intravenously.

variation, 6%). Administration of the second dose had no additional effect. No significant change was noted in QT_c interval in the vehicle-treated or the amiodarone-treated group.

Effect on WCL. No significant effect of the vehicle was observed. Amiodarone 5 mg/kg increased WCL so that maximal changes were observed after 10 min when WCL was increased by 31% (from 187 ± 8 to 245 ± 19 ms, $p < 0.01$). Administration of a second dose of 5 mg/kg prolonged WCL still further, so that at the end of the experimental protocol, WCL was increased by 81% (from 187 ± 8 to 338 ± 26 ms, $p < 0.01$).

Effect on AERP. A slight (10%), nonsignificant increase was noted in AERP in the vehicle-treated group. Amiodarone 5 mg/kg increased AERP significantly. After 10 min, AERP was prolonged by 13% (from 138 ± 5 to 157 ± 6 ms, $p < 0.05$). Further administration of 5 mg/kg increased AERP further; after 10 min, AERP was prolonged by 18% (from 138 ± 5 to 163 ± 7 ms, $p < 0.001$).

Effect on AVNERP. No significant changes were noted in the vehicle-treated group. Amiodarone 5 mg/kg increased AVNERP significantly. A maximal increase of 19% was noted at the end of the first observation period (from 164 ± 9 to 194 ± 19 ms, p

< 0.05). Further administration of 5 mg/kg increased AVNERP significantly; at the end of the experimental protocol, it was prolonged by 65% (from 164 ± 9 to 271 ± 27 ms, $p < 0.05$).

Effect on VERP. A slight, progressive, and significant increase in VERP was noted in the control group; at the end of the study period, VERP was prolonged by 10% (from 142 ± 9 to 156 ± 7 ms, $p < 0.05$). Amiodarone 5 mg/kg increased VERP by 11% after 30 min from 152 ± 5 to 168 ± 7 ms ($p < 0.01$). Administration of a second dose of amiodarone prolonged VERP still further; at the end of the study period, VERP was prolonged by 20% (from 152 ± 5 to 181 ± 6 ms, $p < 0.001$).

Electrophysiological effects of SR 33589

The electrophysiological effects of SR 33589 are shown in Table 3 and Figs. 3-5.

Effect on SCL. Administration of all three doses of SR 33589 induced slight (5-6%), nonsignificant transient shortening of SCL that within seconds became significant and long-lasting prolongation. The prolongation was dose dependent. SCL was prolonged by 19% ($p < 0.05$) with 1 mg/kg SR 33589, by 29% ($p < 0.01$) by 2.5 mg/kg SR 33589, and by 48% ($p < 0.001$) by 5 mg/kg SR 33589. In all cases, ad

FIG. 5. Electrophysiological changes observed after administration of 5 + 5 mg/kg SR 33589 intravenously. Results presented as in Fig. 2.

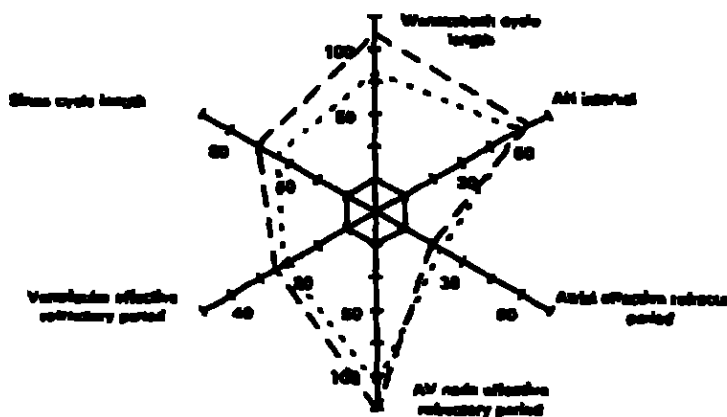


TABLE 1. Effect of administration of vehicle on electrophysiological parameters measured in anesthetized dogs

Parameter	Vehicle				
	4 ml		+4 ml		+90 min
	+10 min	+30 min	+10 min	+30 min	
SCL	2	5	12	19	14
HR	-4	-7	-12	-18	-12
AH	0	-2	2	4	-1
HV	4	3	2	4	6
Wenckebach CL	1	0	-1	2	5
AERP					
Func.	-2	1	1	0	0
EE	0	7	9	2	10
AVNERP					
Rel.	2	2	0	1	2
Func.	1	3	4	5	9 ^a
EE	-2	3	3	-9	0
VERP					
Func.	2	5	4	8 ^a	8 ^a
EE	1	5 ^a	3	6 ^a	10 ^a
Lead II					
PQ	-2	0	2	1	2
QRS	1	3	4	4	4
QT	3	6 ^a	8	10	14 ^a
QTc	1	5	2	1	7

SCL, sinus cycle length; HR, heart rate; AERP, Func., functional; EE, effective; AVNERP, and VERP, atrial, atrioventricular, and ventricular refractory periods; Rel., relative.

Values are mean percentage change.

^a $p < 0.05$ and ^b $p < 0.01$, significant difference from control group.

ministration of the second dose of SR 33589 increased the prolongation caused by the first dose.

Effect on AH interval. SR 33589 at 1 mg/kg significantly lengthened AH interval by 16% (from 80 ± 3 to 93 ± 3 ms, $p < 0.01$) immediately after administration. Administration of the second dose of 1 mg/kg had no additional effect. SR 33589 at 2.5 mg/kg caused immediate prolongation of the AH interval; 20 min after the first injection, AH interval prolonged by 26% (from 90 ± 4 to 114 ± 4 ms, $p < 0.01$). This prolongation lasted throughout the experimental period. SR 33589 at 5 mg/kg also increased the AH interval; 7 min after administration AH interval was prolonged by 60% (from 81 ± 5 to 129 ± 12 ms, $p < 0.01$). After administration of the second 5-mg/kg dose, the AH interval was prolonged by 65% after 10 min (from 81 ± 5 to 133 ± 9 ms, $p < 0.001$).

Effect on HV interval. Administration of both doses of 1 mg/kg SR 33589 and the first dose of 2.5 mg/kg had no marked effect on HV. However, administration of the second dose of SR 33589 prolonged HV interval by ~15% (after 60 min; from 23 ± 3 to 26 ± 3 ms, $p < 0.05$). SR 33589 at 5 mg/kg had no significant effect on HV interval. Administration of the second dose of 5 mg/kg induced slightly

greater prolongation of HV interval; 30 min after injection, HV interval was increased by 15% (from 22 ± 1 to 25 ± 1 ms, $p < 0.05$).

Effect on PQ, QRS, and QTc intervals. SR 33589 at 1 mg/kg significantly prolonged PQ interval; after 8 min, PQ interval was prolonged by 10% (from 113 ± 5 to 125 ± 5 ms, $p < 0.01$). Administration of the second dose of 1 mg/kg had no additional effect. At 2.5 mg/kg, SR 33589 caused an immediate and relatively large increase in PQ interval; 40 min after administration of the first dose, the PQ interval was prolonged by 18% (from 111 ± 5 to 131 ± 9 ms, $p < 0.05$) and was prolonged further by administration of the second dose. A maximal effect was observed after 30 min: PQ interval was prolonged by 25% (from 111 ± 5 to 139 ± 8 ms, $p < 0.001$). Administration of 5 mg/kg also prolonged PQ interval progressively and significantly; after 8 min, it was prolonged by 44% (from 108 ± 4 to 156 ± 14 ms, $p < 0.01$). After administration of the second dose, PQ interval was prolonged further; maximal effect was noted after 7 min when PQ interval was prolonged by 51% (from 108 ± 4 to 163 ± 11 ms, $p < 0.01$).

As in the vehicle-treated group, SR 33589 at mg/kg slightly but significantly lengthened the QR complex; after 60 min, QRS duration was prolonged by 10% (from 34 ± 2 to 37 ± 2 ms, $p < 0.05$). similar trend was evident after administration of 1)

TABLE 2. Effect of administration of amlodipine on electrophysiological parameters measured in anesthetized dogs

Parameter	Amlodipine				
	5 mg/kg		+5 mg/kg i.v.		r
	+10 min	+30 min	+10 min	+30 min	
SCL	13 ^a	26	33	51 ^a	-
HR	-12 ^a	-19 ^a	-23	-32 ^a	-
AH	13	9	14	18 ^a	-
HV	9	12	14	15	-
Wenckebach CL	31 ^a	31 ^a	58 ^a	61 ^a	-
AERP					
Func.	13 ^a	9 ^a	17 ^a	14 ^a	-
EE	13 ^a	10 ^a	18 ^a	14 ^a	-
AVNERP					
Rel.	4	5	7 ^a	5	-
Func.	19 ^a	17 ^a	35 ^a	43 ^a	-
EE	26	19 ^a	49 ^a	64 ^a	-
VERP					
Func.	6	9 ^a	15 ^a	17 ^a	-
EE	6 ^a	11 ^a	17 ^a	19 ^a	-
Lead II					
PQ	11	7	12	12	-
QRS	-1	3 ^a	4	4	-
QT	5	17 ^a	15 ^a	24 ^a	-
QTc	-2	1	0	1	-

Abbreviations as in Table 1.

Values are mean percentage change.

^a $p < 0.05$, ^b $p < 0.01$, ^c $p < 0.001$, significant difference from control group.

ELECTROPHYSIOLOGICAL ACTIONS OF SR 33589

TABLE 3. Effect of administration of SR 33589 on electrophysiological parameters measured in anesthetized dogs

Parameter	SR 33589														
	1 mg/kg			+1 mg/kg i.v.			2.5 mg/kg			+2.5 mg/kg i.v.			5 mg/kg		
	10 min	50 min		+10 min	+50 min	+90 min	10 min	50 min		+10 min	+50 min	+90 min	10 min	50 min	
WCL	12 ^a	19 ^b		15 ^a	27 ^b	20	12 ^b	29 ^a		31 ^a	45 ^a	53 ^a	36 ^a	48 ^a	59 ^a
IR	-12 ^a	-17 ^b		-15 ^b	-23 ^b	-15	-10 ^b	-21 ^c		-23 ^c	-30 ^c	-34 ^c	-27 ^c	-31 ^c	-36 ^c
ΔH	12 ^b	8		12 ^a	15 ^b	11 ^c	23 ^a	24 ^a		34 ^a	30 ^a	32 ^a	60 ^a	49 ^a	51 ^a
HV	-4	-4		-2	-4	-5	4	4		9 ^b	10 ^b	11 ^b	1	3	12
Wenckebach CL	13 ^a	10 ^b		31 ^a	33 ^a	30 ^b	42 ^c	44 ^c		75 ^c	78 ^c	95 ^b	83 ^c	78 ^c	112 ^c
AERP															
Func.	4 ^a	4 ^a		10 ^a	8	10	15 ^a	12 ^a		19 ^a	22 ^a	23 ^a	15 ^a	9 ^a	11 ^b
EH	8 ^b	8 ^b		12 ^b	9	12 ^b	17 ^c	16 ^c		18 ^b	22 ^b	23 ^b	19	8	14
AVNERP															
Rel.	3	0		3	2	1	11 ^b	10		8	12 ^b	12 ^b	15	14	16
Func.	10 ^a	9		17 ^a	17 ^a	15	30 ^a	30 ^a		49 ^a	50 ^a	52 ^a	59 ^a	44 ^b	66 ^a
EH	10	5		15	21	22	53 ^a	63 ^a		99 ^a	99 ^a	94 ^a	103 ^a	96 ^a	125 ^a
VERP															
Func.	7	9		10	11 ^b	14	8 ^b	12 ^b		14 ^a	19 ^a	21 ^c	7	8	13 ^b
EH	2	5		7 ^b	4	8	12 ^a	15 ^a		18 ^a	23 ^a	23 ^a	20 ^a	22 ^a	23 ^a
Lead II															
PQ	8 ^b	4 ^b		9	11 ^c	6	19 ^a	16 ^a		23 ^a	23 ^a	25 ^a	42 ^a	35 ^a	51 ^a
QRS	9 ^b	9 ^b		8	9 ^b	9	0	2		4 ^b	4	5	4 ^b	4	6
QT	3	8 ^a		9 ^a	12 ^a	13 ^b	3	17 ^a		15 ^a	27 ^a	35 ^a	7 ^a	17 ^a	19 ^a
QTc	-3	-2		1	-1	3	-2	4		0	5 ^b	9 ^a	-9 ^a	-4	-6 ^a

Abbreviations as in Table 1.
Values are mean percentage change.
^a p < 0.01, ^b p < 0.05, and ^c p < 0.001, significant difference from control group.

second dose. At 2.5 mg/kg, SR 33589 had no significant effect on QRS duration, but administration of the second dose (2.5 mg/kg) slightly but significantly increased QRS duration (9%, from 35 ± 2 to 38 ± 2 ms, p < 0.05). This increase was the same as that for the vehicle-treated group. At 5 mg/kg, SR 33589 similarly lengthened the QRS complex to a degree similar to that in the vehicle-treated group (4%, from 33 ± 3 to 34 ± 2 ms, p < 0.05). The second dose did not significantly alter this measurement.

At 1 mg/kg SR 33589 followed by a second dose of 1 mg/kg, did not affect QTc interval. Neither did administration of 2.5 mg/kg SR 33589 cause any change. The second dose of 2.5 mg/kg at the end of the observation period slightly but significantly lengthened QTc interval (9%, from 360 ± 15 to 392 ± 17 ms, p < 0.01). At 5 mg/kg, SR 33589 significantly decreased QTc interval; after 10 min, it was reduced by 9% (from 361 ± 9 to 330 ± 6 ms, p < 0.01). The second dose had no additional effect.

Effect on WCL. WCL was greatly increased by 1 mg/kg WCL (13% from 183 ± 18 to 207 ± 17 ms, p < 0.01) 10 min after administration of SR 33589. A second dose of 1 mg/kg increased WCL further (33%, from 183 ± 18 to 243 ± 23 ms, p < 0.01). At 2.5 mg/kg WCL was considerably increased; after 50 min, it was increased by 44% (from 220 ± 11 to 317 ± 22 ms, p < 0.001). Administration of the second dose of SR 33589 caused greater prolongation of WCL; at the end of the experimental protocol

WCL was increased by 95% (from 220 ± 11 to 428 ± 61 ms, p < 0.05). Administration of 5 mg/kg SR 33589 increased WCL by 83% (from 203 ± 16 to 372 ± 22 ms, p < 0.001). Administration of a second dose of 5 mg/kg increased WCL further; after 10 min, WCL was maximally prolonged (112%, from 203 ± 16 to 432 ± 29 ms, p < 0.001).

Effect on AERP. Administration of 1 mg/kg SR 33589 increased AERP by 8% after 50 min (from 128 ± 4 to 138 ± 3 ms, p < 0.05). The second dose of 1 mg/kg increased AERP slightly more; after 90 min it prolonged by 12% (from 128 ± 4 to 143 ± 3 ms, p < 0.05). At 2.5 mg/kg, SR 33589 increased AERP after 50 min by 16% (from 146 ± 10 to 170 ± 9 ms, p < 0.001). Further administration of 2.5 mg/kg increased AERP further; at the end of the experimental period, AERP was increased by 23% (from 146 ± 10 to 180 ± 12 ms, p < 0.05). At 5 mg/kg, SR 33589 increased AERP by 19% after 10 min (from 140 ± 6 to 167 ± 8 ms, NS). The second dose had no additional effect.

Effect on AVNERP. Administration of 1 mg/kg SR 33589 caused a nonsignificant increase in AVNERP (10%) after 10 min. Administration of the second dose of SR 33589 caused greater (22%) but still nonsignificant prolongation of AVNERP. At 2.5 mg/kg, SR 33589 increased AVNERP by 63% at the end of the study (from 171 ± 9 to 278 ± 24 ms, p < 0.01). Administration of the second dose of SR 33589 caused greater prolongation of AVNERP; after 10 min, it was increased by 99% (from 171 ± 9 to

341 ± 25 ms, $p < 0.001$). At 5 mg/kg, SR 33589 increased AVNERP by 105% after 10 min (from 167 ± 5 to 341 ± 19 ms, $p < 0.001$). The second dose induced a slightly greater increase in AVNERP; after 10 min, it was prolonged by 125% (from 167 ± 5 to 374 ± 11 ms, $p < 0.001$).

Effect on VERP. At 1 mg/kg, SR 33589 did not significantly increase VERP (maximal change ~5% after 50 min), but 2.5 mg/kg SR 33589 increased VERP by 15% after 50 min (from 174 ± 13 to 200 ± 11 ms, $p < 0.01$). Administration of a second dose of 2.5 mg/kg increased VERP still further; at the end of the experimental protocol, VERP was increased by 23% to 214 ± 10 ms ($p < 0.01$). At 5 mg/kg, SR 33589 increased VERP by 22% after 50 min (from 160 ± 7 to 195 ± 11 ms, $p < 0.01$). Administration of the second dose of SR 33589 induced an increased VERP slightly more; after 50 min, VERP was prolonged by 25% (from 160 ± 7 to 200 ± 11 ms, $p < 0.05$).

Reverse use-dependence

Reverse use-dependence results are shown in Figs. 6 and 7 as effects at 20, 50, and 80 min after drug administration. A significant reduction in VERP when SCL was reduced was evident in animals before drug administration (from ~160 ms at 400-ms CL to ~135 ms at 200-ms CL).

Administration of amiodarone 5 mg/kg significantly prolonged VERP at slower stimulation frequencies. However, at the highest stimulation frequency, this effect was lost; amiodarone had no effect on VERP at 200-ms stimulation frequency. No true difference was demonstrated between effects at 20, 50, or 80 min.

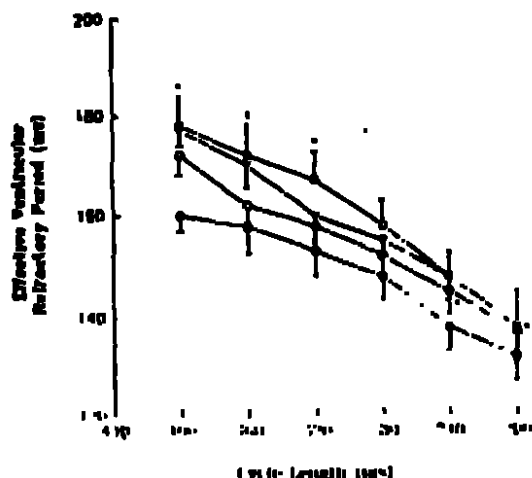


FIG. 8. Use-dependence effects on effective ventricular refractory period after administration of 2.5 mg/kg SR 33589. Results are mean values $\pm$ SEM. * $p < 0.05$, level of statistical difference from predrug values. Predrug (solid circles), 20 min after drug administration (open circles), 50 min after drug administration (solid inverted triangles), 80 min after drug administration (open squares).

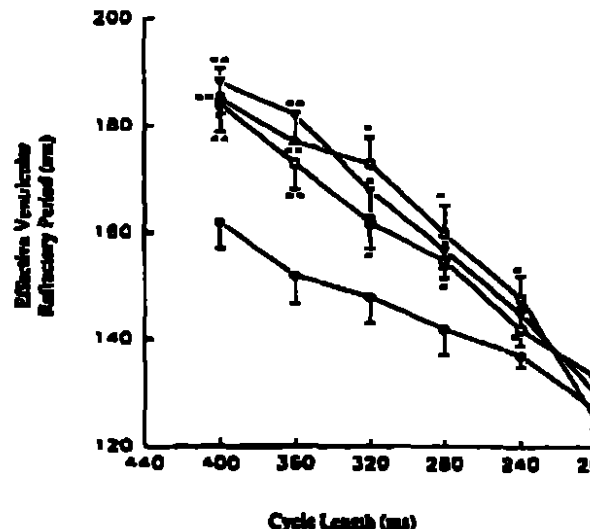


FIG. 7. Use-dependence effects on effective ventricular refractory period after administration of 5 mg/kg amiodarone. Results are mean values $\pm$ SEM. * $p < 0.05$ and ** $p < 0.01$ level of statistical difference from predrug values. Predrug (solid circles), 20 min after drug administration (open circles), 50 min after drug administration (solid inverted triangles), 80 min after drug administration (open squares).

The effects of 2.5 mg/kg SR 33589 tended to increase with time so that prolongation of VERP appeared greater at 80 than at 20 min after administration. As with amiodarone, the absolute degree of prolongation was reduced at the highest frequencies of stimulation (240 and 200 ms). However, SR 33589 still produced significant prolongation of VERP at these CLs. In addition, the percentage of reduction of VERP prolongation was less than that obtained with amiodarone when administered under present study conditions. Thus, SR 33589 has a profile similar to that of amiodarone in the conditions of the present study, with slightly more activity at higher frequencies.

DISCUSSION

Our results show that SR 33589 has an electrophysiological profile similar to that of amiodarone. The greatest modifications produced by acute administration of amiodarone were the increases in SCL (reduced HR), AVNERP, and WCL. There were concomitant significant increases in AVN and VERP and AH interval. In comparison to effects in the vehicle-treated group, acute administration of amiodarone with the dosage regimen used in the present study (5 + 5 mg/kg) had no drug effect on HV, PQ, QRS, or QTc intervals.

Like amiodarone, SR 33589 produced the greatest increases in three parameters: SCL, AVNERP, and WCL. Significant increases in SCL and AVNERP were observed after administration of 1 + 1 mg/kg of the agents. After administration of 2.5 + 2.5 mg/kg SR 33589, the effect on AVNERP was:

84

ELECTROPHYSIOLOGICAL ACTIONS OF SR 33589

259

more marked. In addition, with this dose regimen, SR 33589 prolonged VERP, AERP, and PQ interval. To a lesser extent, HV interval and QTc interval were prolonged with this dose regimen. Most parameters (SCL, AH, PQ, WCL, and AVNRP) exhibited a progressive increase after administration of the three different dose regimens of SR 33589. Administration of the second dose of amiodarone also increased prolongation of these parameters further. Because SR 33589 at 2.5 ± 2.5 mg/kg induced increases in these parameters similar to or greater than those induced by amiodarone 5.0 ± 5.0 mg/kg, SR 33589 and amiodarone apparently have similar electrophysiological profiles.

With both amiodarone and SR 33589 in this study, slow onset of action was apparent; the alterations noted were often not maximal until near the end of the experimental protocol (90 min). This action is well known for amiodarone and would be expected of any amiodarone-like agent such as SR 33589. Therefore, we selected a relatively long complex protocol (90 min). When administered with a brief infusion time at high doses, amiodarone can alter cardiovascular function significantly. Thus, clinically, amiodarone is often administered first as a bolus, followed by infusion of a second dose (19,20). To limit any profound effects of amiodarone on hemodynamic function and to mimic better clinical conditions, we also used a two-stage drug administration procedure; which also allowed us to measure in the same study the effect of a single dose of both agents over a relatively long time course followed by a second cumulative dose when the effects of the initial dose had stabilized.

The effects of SR 33589 on HR and VERP certainly represent efficient mechanisms for suppression of both reentry and enhanced automaticity-induced arrhythmias combined with significant prolongation of AVNRP period that would limit underlying ventricular rate during atrial fibrillation. Neither amiodarone nor SR 33589 prolonged greatly QTc when administered acutely in the study conditions. SR 33589 prolonged QTc by a maximum of 9% at 90 min after administration, and no significant change was observed with amiodarone. Although the changes in QTc were minimal (maximum 9%) with either agent, the increase in VERP was much greater. The reason for this disparity is not clear, but the increase appeared to be qualitatively similar for both amiodarone and SR 33589. In contrast to our results obtained with acute administration, long-term administration of amiodarone is normally considered to prolong QTc (21). The lack of any marked effect on HV and QRS intervals suggests that conduction velocity in ventricular tissue may not be modified by these agents after acute administration to anesthetized dogs. However, our recent, as-yet-unpublished studies (A. S. Manning, unpublished observations) showed significant pro-

longation of HV interval with a much less marked effect on PQ interval after i.v. administration of either amiodarone or SR 33589 to pigs. In contrast, a much greater effect on PQ interval (in comparison to our results) was noted when amiodarone or SR 33589 was given orally to conscious dogs. Thus, although experimental conditions, species, and mode of drug administration may all influence the electrophysiological characteristics of a drug, both SR 33589 and amiodarone appear to have a similar electrophysiological pattern of activity that is partly dependent on experimental conditions.

Recently, many new agents have been entered in clinical trials for development as potential antiarrhythmic agents. Many of these compounds, such as D-sotalol, E-4031, UK-66,914, and UK-68,798, prolong ventricular refractoriness by block of one or more repolarizing potassium currents (22-25). The effects of these agents has been shown to diminish substantially when stimulation frequency increases: At high stimulation frequencies, the mechanism by which these agents act to suppress arrhythmia formation is no longer functional. This process, termed reverse use-dependence, was suggested to be a serious limitation to the antiarrhythmic efficacy of all "pure" class III antiarrhythmic agents acting through this process (26). In addition, Hondeghem (26) also suggested that reverse use-dependency is responsible for a high incidence of proarrhythmic effects (torsades de pointes) noted with this type of antiarrhythmic agent. Our results with SR 33589 indicate that when stimulation frequency is raised as high as is practically possible in anesthetized dogs without causing arrhythmias directly, it still prolongs VERP significantly. The exact magnitude of prolongation appears to be slightly less than that observed at low stimulation frequencies but the potentially beneficial effect is evident. In addition, the degree of reduction of refractory period prolongation was not excessive; amiodarone appeared to lose more activity at shorter CL. With regard to refractory period, prolongation at long CL has often been suggested to be a potential cause of torsades de pointes. Prolongation of VERP by SR 33589 was not excessive in this study and may well be insufficient to act as a proarrhythmic mechanism; however, this result was obtained after acute administration of SR 33589 and amiodarone. Much of the potential antiarrhythmic activity of amiodarone is observed only after chronic administration. Indeed, a previous study (6) has suggested that amiodarone, chronically administered, does not result in reverse use-dependence; unlike other class III antiarrhythmic agents. If this is indeed true, it implies that other antiarrhythmic agents structurally related to amiodarone may also demonstrate enhanced activity after chronic administration.

SR 33589 has been shown to be a potent anti-

54

rhythmic agent in different circumstances and experimental conditions. For example, we have recently shown (16) that this agent reduces the incidence of life-threatening arrhythmias that arise during either acute coronary artery occlusion or reperfusion after transient ischemia in anesthetized rats. Against both these arrhythmia substrates that are responsible for formation of lethal ventricular arrhythmias, SR 33589 was effective at lower doses than those shown to be necessary with amiodarone. In a separate study (17), we showed that SR 33589 can significantly reduce the incidence of ventricular fibrillation occurring during a period of acute coronary artery ligation in open-chest, anesthetized pigs. Again this occurred at lower doses than those shown to be necessary with amiodarone. In both the pig and rat studies, the minimal active dose of SR 33589 was ~1 mg/kg i.v., the same dose that had some electrophysiological actions in the present study, suggesting possible mechanisms for its antiarrhythmic efficacy. In addition, we recently published the results of an investigation of the relative ability of amiodarone and SR 33589 to prevent atrial fibrillation in dogs (27). Although both agents were shown to be effective, SR 33589 was effective at doses four times lower than that of amiodarone in restoring normal sinus rhythm.

Although amiodarone has been available for clinical use for >30 years, its exact mechanism of action as an antiarrhythmic and antifibrillatory agent is still unknown because it has a range of potential antiarrhythmic properties (2). These include inhibition of both the fast sodium and slow calcium currents (i.e., class I and class IV antiarrhythmic actions), partial noncompetitive inhibition of adrenergic stimulation (class II antiarrhythmic action), and prolongation of APD (class III antiarrhythmic action). All these pharmacologic actions will be antiarrhythmic under certain circumstances. SR 33589 was developed as an amiodarone-like agent in terms of structure (both are substituted benzofurans) and in terms of its pharmacologic profile of activity. We previously showed that SR 33589 has significant antisymphathetic activity in anesthetized dogs, partially inhibiting the effects of both α - and β -adrenergic stimulation (28). In addition, we demonstrated a similar level of inhibition by amiodarone and SR 33589, of both the fast sodium and slow calcium currents (P. Gautier, unpublished observations). Thus, SR 33589 also has all the potential antiarrhythmic mechanisms responsible for amiodarone's clinical activity.

Acknowledgment: We thank the "Institut pour l'Encouragement de la Recherche Scientifique dans l'Industrie et l'Agriculture" (IRSIA) for partial financial support of this work. We also thank A. Haly for secretarial help and J. Houthuys and M. Baetens for expert technical assistance.

REFERENCES

1. Cairns JA, Connolly SJ, Gent M, Roberts R. Post-myocardial infarction mortality in patients with ventricular premature depolarizations. *Circulation* 1991;84:350-7.
2. Gill J, Heel RC, Pilon A. Amiodarone. An overview of its pharmacological properties, and review of its therapeutic use in cardiac arrhythmias. *Drugs* 1992;43:69-110.
3. Pfisterer ME, Kłowski W, Brunner H, Burchhardt D, Burkart F. Long-term benefit of 1 year amiodarone treatment for persistent complex ventricular arrhythmias after myocardial infarction. *Clin Invest* 1993;87:309-11.
4. Polster P, Broekhuysen J. The adrenergic antagonism of amiodarone. *Biochem Pharmacol* 1976;25:131-4.
5. Kadish AH, Chen RF, Schmalz S, Morady F. Magnitude and time course of beta-adrenergic antagonism during oral amiodarone therapy. *Am Coll Cardiol* 1990;16:1240-5.
6. Anderson KP, Walker R, Dussan T, et al. Rate-related electrophysiologic effects of long-term administration of amiodarone on canine ventricular myocardium in vivo. *Circulation* 1989;79:348-58.
7. Li JYM, Northover BJ. Antiarrhythmic and electrophysiological effects of amiodarone, flecainide, and pentamidine in anesthetized rats. *Cardiovasc Res* 1992;26:1116-30.
8. Mason JW, Hondeghem LM, Katzung BG. Block of inactivated sodium channels and of depolarization-induced automaticity in guinea pig papillary muscle by amiodarone. *Circ Res* 1984;55:277-85.
9. Honjo H, Kodama I, Kamijima K, Toyama J. Block of cardiac sodium channels by amiodarone studied by using Vmax action potential in single ventricular myocytes. *Br J Pharmacol* 1991;102:651-6.
10. Nattel S, Tshibye M, Quast M, Deroode M. Frequency-dependent effects of amiodarone on atrioventricular node function and slow-channel action potentials: evidence for calcium channel-blocking activity. *Lab Invest Electrophysiol* 1987;76:442-9.
11. Nishimura M, Fellner CH, Singer DH. Amiodarone blocks calcium current in single guinea pig ventricular myocytes. *Pharmacol Exp Ther* 1985;235:450-8.
12. Haworth RA, Goknur AB, Berkoff HA. Inhibition of A-type potassium channels of adult rat heart cells by antiarrhythmic drugs. *Circ Res* 1989;65:1157-60.
13. Eisner JR, Benveniste PB, Hondeghem LM, Roden DM. Suppression of time-dependent outward current in guinea pig ventricular myocytes. *Circ Res* 1991;69:519-29.
14. Marini WJ, Rosenow EC. Amiodarone pulmonary toxicity: recognition and pathogenesis (part I). *Chest* 1988;93:1075.
15. Duke MD, Madison JM, Montgomery CK. Electron microscopic demonstration of lysosomal inclusion bodies in the liver, lymph nodes, and blood leukocytes of patients with amiodarone pulmonary toxicity. *Am J Med* 1985;78:506.
16. Brynnaert C, Rombout J, Chatelein P, Manning A. SR 33589, a new amiodarone-like agent: effect on reperfusion-induced arrhythmias in anesthetized rats. *J Mol Cell Cardiol* 1992;24:S68.
17. Flammex O, Manning SA, Chatelein P. SR 33589, a new amiodarone-like agent: effect on ischemia-induced ventricular arrhythmias in anesthetized pigs. *Br J Pharmacol* 1993;28P.
18. Bazett HC. An analysis of the time-relations of electric diagrams. *Heart* 1920;7:353-70.
19. Nales PC, Ismail Y, Pappas JM, et al. Intravenous amiodarone for short-term treatment of refractory ventricular tachycardia or fibrillation. *Am Heart J* 1991;122:1629-33.
20. Mosow ND, Rakita L, Vrebal TR, Noon D, Sturmer J. Amiodarone. Intravenous loading for rapid suppression of complex ventricular arrhythmias. *J Am Coll Cardiol* 1984;4:104.
21. Singh BN, et al. The effect of amiodarone, a new antiarrhythmic drug on cardiac muscle. *Br J Pharmacol* 1970;39:657-74.

56

31-703199800=EPO

/44-01937546304=BRITISH L/01-09-19-10:51/002-011

ELECTROPHYSIOLOGICAL ACTIONS OF SR 33589

21

22. Sanginetti MS, Jurkiewicz NK. Two components of cardiac delayed rectifier K⁺ current: differential sensitivity to block by class III antiarrhythmic agents. *J Gen Physiol* 1990; 96:194-214.
23. Wallace AA, Stupieniski RP, Brookes LM, Sebnick HG, Charmon DA, Lynch JJ. Cardiac electrophysiologic and inotropic actions of new and potent methanesulfonamide class III antiarrhythmic agents in anesthetized dogs. *J Cardiovasc Pharmacol* 1991;18:687-95.
24. Carmeliet E. Electrophysiologic and voltage clamp analysis of the effects of sotalol on isolated cardiac muscle and Purkinje fibers. *J Pharmacol Exp Ther* 1985;232:817-25.
25. Gwilt M, Dabrynski HW, Blackburn KJ, Burgess RA, Higgins AJ. UK-66,914—a novel class III antiarrhythmic agent which blocks potassium channels. *Circulation* 1988;78:11-1.
26. Hondeghem LM. Ideal antiarrhythmic agents: classical fibrillators. *J Cardiovasc Electrophysiol* 1991;2:S169-77.
27. Hodge D, Chazotte P, Manning AM. SR 33589—effect on ventricular fibrillation in dogs—comparison with amiodarone. International Society for Heart Research. European Sec Meeting. Montreux Editors, 1994:381-4.
28. Manning AS, Bruyninckx C, Hodge D, Ramackers J, Chazotte P. SR 33589: a new amiodarone-like antiarrhythmic agent. *Br J Pharmacol* 1992;107(suppl):270P.

47

(12) SOLICITUD INTERNACIONAL PUBLICADA SEGÚN EL TRATADO DE COOPERACIÓN DE PATENTES (PCT)

(19) Organización Mundial de Propiedad Intelectual
Oficina Internacional



(43) Fecha de Publicación

Junio 20 de 2002 (20.06.2002)

PCT

(10) Número de Publicación Internacional

WO 02/47660 A1

(51) Clasificación Internacional de Patentes: A61K 9/08,
47/12, 47/40

(21) Número de Solicitud Internacional:

PCT/FR01/03903

(22) Fecha de Registro Internacional: Diciembre 10 de 2001
(10.12.2001)

(25) Idioma de registro: Frances

(26) Idioma de Publicación: Frances

(30) Información de Prioridad:

00/16071 Diciembre 11 de 2000 (11.12.2000) FR

(71) Solicitante: (Para todos los Estados designados excepto Estados Unidos de América): SANOFI-SYNTHELABO [FR/FR]; 174 avenue de France, 75013 Paris (FR)

(72) Inventores; e

(73) Inventores/Solicitantes (para Estados Unidos de América solamente): BOURRIAGUE-SEVE, Frédérique [FR/FR]; Le Village, F-34190 Ferrières les Verreries (FR). BREUL, Thierry [FR/FR]; 118, avenue F. de Lesseps, F-34110 Frontignan (FR).

(74) Agente: THOURET-LEMAITRE, Elisabeth; Sanofi-Synthelabo, 174 avenue de France, F-75013 Paris (FR).

(81) Estados Designados (nacionales): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Estados Designados (regionales): Patente ARIPO (GH, GM, KE, LS, MW, MZ, SD, SI, SZ, TZ, UG, ZM, ZW), patente Eurasiática (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM) Patente Europea (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), Patente OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Publicado:

- con reporte de búsqueda internacional
- antes de la expiración del límite de tiempo para modificar las reivindicaciones y ser publicada de nuevo en el caso de recibo de modificaciones

Para los códigos de dos letras y otras abreviaturas, véase a "Las Notas Guías sobre Códigos y Abreviaturas" que aparecen al comienzo de cada emisión regular de la Gaceta PCT.

(54) Título:

"COMPOSICION FARMACEUTICA DE DRONEDARONA PARA ADMINISTRACION PARENTERAL"

(57) Resumen: La invención tiene por objeto una composición farmacéutica para administración parenteral, caracterizada porque comprende: la dronedarona o una de sus sales farmacéuticamente aceptables como principio activo; una solución tampón fisiológicamente aceptables capaz de mantener el pH de la composición entre 3 y 5; un derivado hidrosoluble de β -ciclodextrina fisiológicamente aceptable.

(19) Organisation Mondiale de la Propriété
Intellectuelle
Bureau international



(43) Date de la publication internationale
20 juin 2002 (20.06.2002)

PCT

(10) Numéro de publication internationale
WO 02/47660 A1

(51) Classification internationale des brevets⁷ : A61K 9/08,
47/12, 47/40

(21) Numéro de la demande internationale :
PCT/FR01/03903 ✓

(22) Date de dépôt international :
10 décembre 2001 (10.12.2001)

(25) Langue de dépôt : français

(26) Langue de publication : français

(30) Données relatives à la priorité :
00/16071 11 décembre 2000 (11.12.2000) FR

(81) États désignés (national) : AE, AG, AL, AM, AT, AU, AZ,
BA, BB, BG, BR, BY, BZ, CA, CH, CN, CQ, CR, CU, CZ,
DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM,
HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK,
LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX,
MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI,
SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN,
YU, ZA, ZM, ZW.

(84) États désignés (régional) : brevet ARIPO (GH, GM, KE,
LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), brevet
eurasien (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), brevet
européen (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR,
IE, IT, LU, MC, NL, PT, SE, TR), brevet OAPI (BF, BJ,
CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN,
TD, TG).

(71) Déposant (pour tous les États désignés sauf US) :
SANOFI-SYNTHELABO (FR/FR); 174 Avenue de
France, 75013 Paris (FR).

(72) Inventeurs; et
(75) Inventeurs/Déposants (pour US seulement) : BOUR-
RIAGUE-SEVE, Frédérique (FR/FR); Le Village,
F-34190 Ferrières les Verreries (FR). BREUL, Thierry
(FR/FR); 118, avenue F. de Lesseps, F-34110 Frontignan
(FR).

(74) Mandataire : THOURET-LEMAITRE, Elisabeth;
Sanofi-Synthelabo, 174 avenue de France, F-75013 Paris
(FR).

Publiée :

- avec rapport de recherche internationale
- avant l'expiration du délai prévu pour la modification des
revendications, sera republiée si des modifications sont
reçues

En ce qui concerne les codes à deux lettres et autres abrévia-
tions, se référer aux "Notes explicatives relatives aux codes et
abréviations" figurant au début de chaque numéro ordinaire de
la Gazette du PCT.

(54) Title: PHARMACEUTICAL DRONEDARONE COMPOSITION FOR PARENTERAL ADMINISTRATION

(54) Titre : COMPOSITION PHARMACEUTIQUE DE DRONEDARONE POUR ADMINISTRATION PARENTERALE

(57) Abstract: The invention concerns a pharmaceutical composition for parenteral administration, characterised in that it com-
prises: dronedarone or one of its pharmaceutically acceptable salts as active principle; a physiologically acceptable buffer solution
capable of maintaining the pH of the composition between 3 and 5; a physiologically acceptable water-soluble β -cyclodextrin deriva-
tive.

(57) Abrégé : L'invention a pour objet une composition pharmaceutique pour administration parentérale, caractérisée en ce qu'elle
comprend: la dronedarone ou un de ses sels pharmaceutiquement acceptables en tant que principe actif; une solution tampon phy-
siologiquement acceptable capable de maintenir le pH de la composition entre 3 et 5; un dérivé hydrosoluble de β -cyclodextrine
physiologiquement acceptable.

WO 02/47660 A1

60
57

TRATADO DE COOPERACION DE PATENTES
PCT
REPORTE DE EXAMEN PRELIMINAR INTERNACIONAL

(PCT Artículo 36 y Regla 70)

Registro de referencia del solicitante o agente 1214/MW	PARA FUTURAS ACCIONES Ver Notificación o Transmisión del Reporte de Examen Preliminar Internacional (Formato PCT/IPEA/416)	
Solicitud Internacional No. PCT/FR01/03903	Fecha de registro internacional (día/mes/año) 10/12/2001	Fecha de prioridad (día/mes/año) 11/12/2000
Clasificación Internacional de Patentes (IPC) o clasificación nacional e IPC A61K9/08		
Solicitante SANOFI-SYNTHELABO et al.		

1. Este reporte de examen preliminar internacional ha sido preparado por esta Autoridad Examinadora Preliminar Internacional y se transmite al solicitante de conformidad con el Artículo 36. 2. Este REPORTE consta de un total de <u>4</u> páginas, incluyendo la carátula. ☐ Este reporte también está acompañado de ANEXOS, es decir, páginas de descripción, reivindicaciones y/o dibujos que han sido modificados y son la base de este informe y/o páginas que contienen rectificaciones hechas ante esta Autoridad (ver Regla 70.16 y la Sección 607 de las Instrucciones Administrativas de conformidad con el PCT). Estos anexos constan de un total de páginas.
3. Este reporte contiene indicaciones relacionadas con los siguientes ítems: I ☒ Bases del Reporte II ☐ Prioridad III ☐ No establecimiento de opinión respecto a novedad, nivel inventivo y aplicabilidad Industrial. IV ☐ Falta de unidad de invención V ☒ Afirmación razonada de conformidad con el Artículo 35(2) con respecto a novedad, nivel inventivo o aplicabilidad industrial; citaciones y explicaciones que sustentan dicha afirmación. VI ☐ Ciertos documentos citados VII ☐ Ciertos defectos en la solicitud internacional VIII ☐ Ciertas observaciones sobre la solicitud internacional

Fecha de presentación de la demanda 03/07//2002	Fecha de terminación de este reporte 12.09.2002
Nombre y dirección de la autoridad internacional de examen preliminar: Oficina de Patentes Europea D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Funcionario autorizado Vermeulen, S Teléfono No. +49 89 2399 7520

I. Bases del Reporte

1. Respecto a los elementos de la solicitud internacional: (Páginas de remplazo que han sido suministradas a la oficina receptora en respuesta a una invitación bajo el artículo 14 están referenciados en este reporte como "presentados originalmente" y no están anexos a este reporte dado que no contienen modificaciones (Reglas 70.16 y 70.17):

Descripción, Páginas:

1-11 como se presentaron originalmente

Reivindicaciones, No.:

1-19 como se presentaron originalmente

2. Respecto al idioma, todos los elementos marcados anteriormente estuvieron disponibles o fueron suministrados a esta Autoridad en el idioma en el cual la solicitud internacional fue presentada, a menos que se indique lo contrario bajo este ítem.

Estos elementos estuvieron disponibles o fueron suministrados a esta Autoridad en el idioma, el cual es:

- ☐ el idioma de una traducción suministrada para una búsqueda internacional (según la Regla 23.1 (b)).
☐ el idioma de una publicación de la solicitud internacional (según la Regla 48.3 (b)).
☐ el idioma de la traducción suministrada para el examen preliminar internacional (según las Reglas 55.2 y/o 55.3).

3. Respecto al nucleótido y/o secuencia amino ácida revelado en la solicitud internacional, se llevó a cabo el examen preliminar internacional según el listado de secuencia:

- ☐ contenido en la solicitud internacional en forma escrita.
☐ registrado junto con la solicitud internacional en forma legible por computador.
☐ proporcionado subsiguientemente a esta Autoridad en forma escrita.
☐ proporcionado subaiguientemente a esta Autoridad en forma legible por computador.
☐ Se ha proporcionado la afirmación respecto a la cual el listado de secuencia escrito proporcionado subsiguientemente no va más allá de la revelación en la solicitud internacional según se presentó.
☐ Se ha proporcionado la afirmación respecto a la cual la información presentada en forma legible por computador es idéntica al listado de secuencia escrita.

4. ☐ Las modificaciones han resultado en la cancelación de:

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

**REPORTE DE EXAMEN PRELIMINAR
INTERNACIONAL**

Solicitud internacional No. PCT/FR01/03903

62
59

5. ☐ Este reporte ha sido establecido como si (algunas) de las modificaciones no se hubiesen hecho, ya que se ha considerado que van más allá de la revelación según se presentó, como se indicó en Casilla Suplementaria (Regla 70.2 (c)):

(Cualquier hoja de remplazo que contenga tales modificaciones debe ser referida bajo el ítem 1 y anexada a este reporte.)

6. Observaciones adicionales, si son necesarias:

V. Afirmación razonada bajo el Artículo 35(2) respecto a novedad, nivel inventivo o aplicabilidad industrial; citaciones y explicaciones que sustentan dicha afirmación

1. Afirmación

Novedad (N)	Sí:	Reivindicaciones	1-19
	No:	Reivindicaciones	
Nivel inventivo (IS)	Sí:	Reivindicaciones	1-19
	No:	Reivindicaciones	
Aplicabilidad industrial (IA)	Sí:	Reivindicaciones	1-19
	No:	Reivindicaciones	

- 2. Citaciones y explicaciones**
Ver hoja separada

El problema que la presente invención intenta solucionar es la formulación de una nueva composición inyectable de dronedarona que sea a la vez lo suficientemente concentrada para una utilización terapéutica y desprovista de las desventajas habitualmente observadas con ciertas composiciones que contienen la dronedarona, especialmente una mala tolerancia que se manifiesta bajo la forma de inflamaciones en el sitio de inyección.

La composición farmacéutica definida en la reivindicación independiente 1 trae, de manera sorpresiva, una solución al problema planteado.

A pesar de que los derivados de β -ciclodextrina sean conocidos de manera general como agentes que forman complejos y son capaces de aumentar, en las composiciones farmacéuticas, la solubilidad de principios activos poco solubles, ningún documento del estado del arte anterior divulga o sugiere que los derivados de β -ciclodextrina, cuando están asociados a un medio tampón apropiado, pueden aumentar la solubilidad de la dronedarona y al mismo tiempo asegurar una tolerancia aceptable durante su administración. Por consiguiente, el objeto de la reivindicación 1 es novedoso e implica un nivel inventivo (Artículo 33 (2)-(3) PCT).

Las reivindicaciones 2-19 dependen de la reivindicación 1 y, por consiguiente, también cumplen como tales con los requisitos exigidos por el PCT en cuanto a la novedad y el nivel inventivo se refiere.

TRAITE DE COOPERATION EN MATIERE DE BREVETS

61

Expéditeur: L'ADMINISTRATION CHARGÉE DE
L'EXAMEN PRELIMINAIRE INTERNATIONAL

Destinataire:

THOURET-LEMAITRE Elisabeth
SANOFI-SYNTHELABO
Département Brevets
174 avenue de France
FR-75013 PARIS
FRANCE

16 SEP. 2002

reçu H. L.

PCT

NOTIFICATION DE TRANSMISSION DU
RAPPORT D'EXAMEN PRELIMINAIRE
INTERNATIONAL
(règle 71.1 du PCT)

Date d'expédition
(jour/mois/année) 12.09.2002

Référence du dossier du déposant ou du mandataire
1214/MW

NOTIFICATION IMPORTANTE

Demande internationale No.
PCT/FR01/03903

Date du dépôt international (jour/mois/année)
10/12/2001

Date de priorité (jour/mois/année)
11/12/2000

Déposant
SANOFI-SYNTHELABO et al.

1. Il est notifié au déposant que l'administration chargée de l'examen préliminaire international a établi le rapport d'examen préliminaire international pour la demande internationale et le lui transmet ci-joint, accompagné, le cas échéant, de ces annexes.
2. Une copie du présent rapport et, le cas échéant, de ses annexes est transmise au Bureau international pour communication à tous les offices élus.
3. Si tel ou tel office élu l'exige, le Bureau international établira une traduction en langue anglaise du rapport (à l'exclusion des annexes de celui-ci) et la transmettra aux offices intéressés.

4. RAPPEL

Pour aborder la phase nationale auprès de chaque office élu, le déposant doit accomplir certains actes (dépôt de traduction et paiement des taxes nationales) dans le délai de 30 mois à compter de la date de priorité (ou plus tard pour ce qui concerne certains offices) (article 39.1) (voir aussi le rappel envoyé par le Bureau international dans le formulaire PCT/IB/301).

Lorsqu'une traduction de la demande internationale doit être remise à un office élu, elle doit comporter la traduction de toute annexe du rapport d'examen préliminaire international. Il appartient au déposant d'établir la traduction en question et de la remettre directement à chaque office élu intéressé.

Pour plus de précisions en ce qui concerne les délais applicables et les exigences des offices élus, voir le Volume II du Guide du déposant du PCT.

Afin de décider si l'invention est brevetable ou non, l'office élu peut appliquer des critères additionnels ou différents de ceux sur lesquels se fonde le rapport d'examen préliminaire international (voir articles 27.5, 33.5). Ces critères additionnels peuvent inclure par exemple des exceptions à la brevetabilité, et les exigences concernant l'exposé suffisant de l'invention, la clarté des revendications, et leur fondement sur la description.

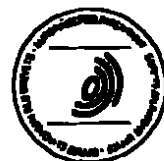
Nom et adresse postale de l'administration chargée de l'examen
préliminaire international

Office européen des brevets
D-80298 Munich
Tél. +49 89 2399 - 0 Tx: 523656 eprmu d
Fax: +49 89 2399 - 4465

Fonctionnaire autorisé

Hutterer, G

Tél. +49 89 2399-8066



2

PCT

RAPPORT D'EXAMEN PRELIMINAIRE INTERNATIONAL

(article 36 et règle 70 du PCT)

Référence du dossier du déposant ou du mandataire 1214/MW	POUR SUITE A DONNER voir la notification de transmission du rapport d'examen préliminaire international (formulaire PCT/PEA/416)	
Demande internationale n° PCT/FR01/03903	Date du dépôt international (jour/mois/année) 10/12/2001	Date de priorité (jour/mois/année) 11/12/2000
Classification internationale des brevets (CIB) ou à la fois classification nationale et CIB A61K9/08		
Déposant SANOFI-SYNTHELABO et al.		

1. Le présent rapport d'examen préliminaire international, établi par l'administration chargée de l'examen préliminaire international, est transmis au déposant conformément à l'article 36.

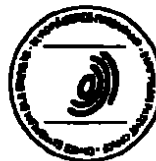
2. Ce RAPPORT comprend 4 feuilles, y compris la présente feuille de couverture.

☐ Il est accompagné d'ANNEXES, c'est-à-dire de feuilles de la description, des revendications ou des dessins qui ont été modifiées et qui servent de base au présent rapport ou de feuilles contenant des rectifications faites auprès de l'administration chargée de l'examen préliminaire international (voir la règle 70.16 et l'instruction 807 des Instructions administratives du PCT).

Ces annexes comprennent feuilles.

3. Le présent rapport contient des indications relatives aux points suivants:

- I ☒ Base du rapport
- II ☐ Priorité
- III ☐ Absence de formulation d'opinion quant à la nouveauté, l'activité inventive et la possibilité d'application industrielle
- IV ☐ Absence d'unité de l'invention
- V ☒ Déclaration motivée selon l'article 35(2) quant à la nouveauté, l'activité inventive et la possibilité d'application industrielle; citations et explications à l'appui de cette déclaration
- VI ☐ Certains documents cités
- VII ☐ Irrégularités dans la demande internationale
- VIII ☐ Observations relatives à la demande internationale

Date de présentation de la demande d'examen préliminaire internationale 03/07/2002	Date d'achèvement du présent rapport 12.09.2002
Nom et adresse postale de l'administration chargée de l'examen préliminaire international:  Office européen des brevets D-80285 Munich Tél. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4485	Fonctionnaire autorisé Vermeulen, S N° de téléphone +49 89 2399 7520 

66
63

RAPPORT D'EXAMEN PRÉLIMINAIRE INTERNATIONAL

Demande internationale n° PCT/FR01/03903

I. Base du rapport

1. En ce qui concerne les éléments de la demande internationale (les feuilles de remplacement qui ont été remises à l'office récepteur en réponse à une invitation faite conformément à l'article 14 sont considérées dans le présent rapport comme "initialement déposées" et ne sont pas jointes en annexe au rapport puisqu'elles ne contiennent pas de modifications (règles 70.16 et 70.17)):

Description, pages:

1-11 version initiale

Revendications, N°:

1-19 version initiale

2. En ce qui concerne la langue, tous les éléments indiqués ci-dessus étaient à la disposition de l'administration ou lui ont été remis dans la langue dans laquelle la demande internationale a été déposée, sauf indication contraire donnée sous ce point.

Ces éléments étaient à la disposition de l'administration ou lui ont été remis dans la langue suivante: , qui est :

- ☐ la langue d'une traduction remise aux fins de la recherche internationale (selon la règle 23.1(b)).
- ☐ la langue de publication de la demande internationale (selon la règle 48.3(b)).
- ☐ la langue de la traduction remise aux fins de l'examen préliminaire internationale (selon la règle 55.2 ou 55.3).

3. En ce qui concerne les séquences de nucléotides ou d'acide aminés divulguées dans la demande internationale (le cas échéant), l'examen préliminaire internationale a été effectué sur la base du listage des séquences :

- ☐ contenu dans la demande internationale, sous forme écrite.
- ☐ déposé avec la demande internationale, sous forme déchiffrable par ordinateur.
- ☐ remis ultérieurement à l'administration, sous forme écrite.
- ☐ remis ultérieurement à l'administration, sous forme déchiffrable par ordinateur.
- ☐ La déclaration, selon laquelle le listage des séquences par écrit et fourni ultérieurement ne va pas au-delà de la divulgation faite dans la demande telle que déposée, a été fournie.
- ☐ La déclaration, selon laquelle les informations enregistrées sous déchiffrable par ordinateur sont identiques à celles du listage des séquences Présenté par écrit, a été fournie.

4. Les modifications ont entraîné l'annulation :

- ☐ de la description, pages :
- ☐ des revendications, n° :
- ☐ des dessins, feuilles :

4

67
64

**RAPPORT D'EXAMEN
PRÉLIMINAIRE INTERNATIONAL**

Demande internationale n° PCT/FR01/03903

5. ☐ Le présent rapport a été formulé abstraction faite (de certaines) des modifications, qui ont été considérées comme allant au-delà de l'exposé de l'invention tel qu'il a été déposé, comme il est indiqué ci-après (règle 70.2(c)) :

(Toute feuille de remplacement comportant des modifications de cette nature doit être indiquée au point 1 et annexée au présent rapport)

6. Observations complémentaires, le cas échéant :

V. Déclaration motivée selon l'article 35(2) quant à la nouveauté, l'activité inventive et la possibilité d'application industrielle; citations et explications à l'appui de cette déclaration

1. Déclaration

Nouveauté	Oui : Revendications 1-19
	Non : Revendications
Activité inventive	Oui : Revendications 1-19
	Non : Revendications
Possibilité d'application industrielle	Oui : Revendications 1-19
	Non : Revendications

- 2. Citations et explications
voir feuille séparée**

3

68
65

RAPPORT D'EXAMEN

Demande internationale n° PCT/FR01/03903

PRELIMINAIRE INTERNATIONAL - FEUILLE SEPARÉE

Le problème que la présente invention tente de résoudre est la formulation d'une nouvelle composition injectable de dronédarone qui soit à la fois suffisamment concentrée pour une utilisation thérapeutique et dépourvue des désavantages observés habituellement avec des compositions contenant de la dronédarone, notamment une mauvaise tolérance qui se manifeste sous forme d'inflammations au site d'injection.

La composition pharmaceutique définie dans la revendication indépendante 1 apporte de manière surprenante une solution au problème posé.

Malgré que les dérivés de β -cyclodextrine soient connus de manière générale comme agents complexant capables d'augmenter dans des compositions pharmaceutiques la solubilité de principes actifs peu solubles, aucun des documents d'art antérieur ne divulgue ni ne suggère que les dérivés de β -cyclodextrine, lorsqu'ils sont associés à un milieu tampon approprié, sont capables d'augmenter la solubilité de la dronédarone tout en assurant une tolérance acceptable lors de son administration. Par conséquent l'objet de la revendication 1 est nouveau et implique une activité inventive (Article 33 (2)-(3) PCT).

Les revendications 2-19 dépendent de la revendication 1 et satisfont donc également, en tant que telles, aux conditions requises par le PCT en ce qui concerne la nouveauté et l'activité inventive.

6

**"COMPOSICION FARMACEUTICA DE DRONEDARONA PARA
ADMINISTRACION PARENTERAL"**

RESUMEN - OBJETO Y FINALIDAD DE LA INVENCION

La invención tiene por objeto una composición farmacéutica para administración parenteral, caracterizada porque comprende: la dronedarona o una de sus sales farmacéuticamente aceptables como principio activo; una solución tampón fisiológicamente aceptable capaz de mantener el pH de la composición entre 3 y 5; un derivado hidrosoluble de β -ciclodextrina fisiológicamente aceptable.

Fig. ninguna

**COMPOSICION FARMACEUTICA DE DRONEDARONA PARA ADMINISTRACION
PARENTERAL**

La presente invención se refiere, de una manera general, a una nueva composición farmacéutica que contiene como principio activo un derivado de benzoil-benzofurano.

En particular, la invención se refiere a una composición farmacéutica para administración parenteral que contiene como principio activo el 2-butil-3-(4-[[3-(dibutilamino)propoxi]] benzoil)-5-metansulfonamido-benzofurano igualmente denominado dronedarona, o una de sus sales farmacéuticamente aceptables preferentemente su clorhidrato.

Este derivado de metansulfonamido-benzofurano así como sus sales farmacéuticamente aceptables fueron descritos en la patente EP 0471609 lo mismo que sus aplicaciones terapéuticas.

En el campo cardio-vascular, este compuesto se muestra particularmente interesante especialmente como agente anti-arritmico.

La dronedarona, bajo forma de su clorhidrato, presenta una solubilidad limitada en medio acuoso: a temperatura ambiente, es de 0,5 mg/ml con pH = 4,85. Dentro de la gama de pH que va de 1,5 a 5, esta solubilidad es prácticamente constante pues se vuelve casi despreciable con pH superiores a 5,5.

Sin embargo, la solubilidad del clorhidrato de dronedarona aumenta en presencia de un tampón fosfato monosódico (NaH_2PO_4): a temperatura ambiente, varía de 2mg/ml

a 2,25 mg/ml en la gama de pH que va de 1,5 a 5 mientras que disminuye brutalmente para volverse casi nula con pH = 5,5.

Test efectuados sobre rata durante varios días con una formulación acuosa conteniendo 1,065 mg/ml de clorhidrato de dronedarona en presencia de un tampón fosfato han mostrado sin embargo una mala tolerancia local de esta composición en contraposición con una formulación idéntica exenta de ese clorhidrato.

Por otra parte, la dronedarona está dotada de propiedades tensioactivas iónicas potentes que provocan, en solución acuosa, una marcada disminución de la tensión superficial. Este carácter tensioactivo se revela en primer lugar tan potente en presencia como en ausencia de un tampón fosfato y puede tenerse como parcialmente responsable de una auto-agregación de las moléculas de dronedarona en solución acuosa. En realidad, esta organización supra-molecular en solución se debe a la formación de dímeros dispuestos pies contra cabeza y apilados en capas superpuestas. Estos dímeros, en el momento de su administración por inyección, provocan la ruptura de la membrana celular y, como consecuencia, la aparición de inflamaciones en el lugar de inyección. De modo general, las propiedades tensioactivas de la dronedarona pueden considerarse como responsables de una mala tolerancia de la composición que la contiene.

En la patente estadounidense N° 4727064 se ha expuesto,

que soluciones acuosas de derivados de ciclodextrina especialmente la hidroxipropil- β -ciclodextrina son capaces de aumentar la solubilidad de principios activos medicamentosos, estas soluciones de derivados de ciclodextrina no provocan irritación local. No obstante, no se encuentra ninguna indicación con respecto a la tolerancia local de tales soluciones de derivados de β -ciclodextrina que contengan igualmente un principio activo medicamentoso.

Dentro del marco de la invención, se ha emitido la hipótesis que derivados de ciclodextrina presentes en una formulación acuosa de dronedarona, bajo forma, por ejemplo, de su clorhidrato, podrían mejorar la tolerancia de este principio activo durante una administración parenteral.

Dentro de esta óptica, se han efectuado test sobre rata durante varios días con una formulación acuosa que contenía 1,065 mg/ml de clorhidrato de dronedarona en presencia de un derivado de ciclodextrina, en este caso la hidroxipropil- β -ciclodextrina. Sin embargo, la administración de una composición semejante ha mostrado una marcada intolerancia en el lugar de inyección en tanto que una formulación idéntica, no obstante exenta de clorhidrato de dronedarona, se ha revelado como bien tolerada.

La búsqueda de una formulación inyectable de dronedarona, de preferencia bajo forma de una de sus sales farmacéuticamente aceptables tal como su clorhidrato, que sea

a la vez suficientemente concentrada para una utilización terapéutica y desprovista de las desventajas informadas precedentemente tiene por consiguiente un interés indiscutible.

Ahora se ha descubierto, de manera sorprendente de acuerdo con la invención, que es posible disponer de soluciones acuosas de dronedarona, en particular bajo forma de su clorhidrato, a la vez concentradas y provistas de una tolerancia aceptable en el momento de su administración.

De hecho, se ha podido evidenciar que los derivados de β -ciclodextrina, cuando están asociados a un medio tampón apropiado, son capaces de aumentar la solubilidad de la dronedarona o de sus sales farmacéuticamente aceptables y de prevenir su auto-agregación.

En consecuencia, la invención se refiere a una composición farmacéutica para administración parenteral que comprende:

- . la dronedarona o una de sus sales farmacéuticamente aceptables como principio activo,
- . una solución tampón fisiológicamente aceptable capaz de mantener el pH de la composición entre 3 y 5,
- . un derivado hidrosoluble de β -ciclodextrina fisiológicamente aceptable.

En la continuación de la descripción lo mismo que en las reivindicaciones y salvo indicaciones en contrario, los

74
71

porcentajes de los diferentes constituyentes que forman las composiciones de la invención a saber el principio activo, el medio tampón, el derivado de β -ciclodextrina o cualquier otro ingrediente complementario, expresan todas proporciones ponderales a saber de % en peso de la composición final.

La dronedarona, preferencialmente bajo forma de una de sus sales farmacéuticamente aceptables por ejemplo el clorhidrato, está presente en las composiciones de la invención a razón de 0,01% a 4% por ejemplo a razón de 0,1% a 0,8%. Sin embargo, las composiciones preferidas contienen de 0,4% a 0,8% de dronedarona o de una de sus sales farmacéuticamente aceptables.

En general, se elige la solución tampón entre soluciones acuosas fisiológicamente aceptables capaces a la vez de disolver el principio activo y de mantener el pH de las composiciones entre 3 y 5.

De esta manera, soluciones tampones utilizables dentro del marco de la invención pueden ser por ejemplo soluciones acuosas que contengan un sistema tampón seleccionado entre los siguientes:

- . ácido acético/acetato de metal alcalino,
- . ácido fumárico/fumarato de metal alcalino,
- . ácido succínico/succinato de metal alcalino,
- . ácido cítrico/citrato de metal alcalino,
- . ácido tártrico/tartrato de metal alcalino,

75
72

- . ácido láctico/lactato de metal alcalino,
- . ácido maleico/maleato de metal alcalino,
- . ácido metansulfónico/metansulfonato de metal alcalino,
- . fosfato monometálico alcalino,

el metal alcalino en cada una de las sales mencionadas precedentemente es, por ejemplo, sodio o potasio.

Con carácter preferencial, se utiliza como tampón un fosfato monometálico alcalino por ejemplo el fosfato monosódico o monopotásico. Este tampón es capaz de mantener el pH de la composición a 4,5, pH a partir del cual un aumento del mismo provoca una disminución drástica de la solubilidad acuosa de la dronedarona en particular de su clorhidrato.

En la mayoría de los casos, la fuerza iónica de la solución tampón estará comprendida entre 0,005 molar y 0,5 molar, de preferencia entre 0,01 y 0,2 molar, por ejemplo de 0,05 a 0,15 molar. Más allá de 0,5 molar, la concentración en sales en el medio amenaza perturbar la estabilidad de las composiciones de la invención y de ocasionar una hipertonia de las formulaciones cuando en una concentración inferior a 0,005 molar el efecto tampón se vuelve inexistente.

A título de ejemplo, se pueden citar soluciones acuosas tampones 0,05 a 0,15 molar en fosfato monometálico alcalino por ejemplo, monosódico o monopotásico.

En cuanto al derivado hidrosoluble de β -ciclodextrina,

se lo elige entre compuestos de este tipo fisiológicamente aceptables, siendo este derivado generalmente más soluble en el agua que la misma β -ciclodextrina. Esta última se ha revelado además inutilizable en razón de su baja solubilidad acuosa y de su toxicidad.

A título de ejemplo de derivados de β -ciclodextrina utilizables en las composiciones de la invención, se puede citar el derivado sulfobutíl éter de β -ciclodextrina, la dimetil β -ciclodextrina, la trimetil β -ciclodextrina así como sus mezclas. No obstante, se prefiere utilizar la hidroxipropil β -ciclodextrina.

En general, el derivado de β -ciclodextrina es incorporado en las composiciones parenterales a razón de 0,5% a 50%, de preferencia de 1 a 10%, por ejemplo 5% y de 5 a 20 veces el peso de dronedarona o de una de sus sales farmacéuticamente aceptables, preferentemente de 10 a 15 veces ese peso y más particularmente de 12 a 13 veces ese peso.

Como se indicara precedentemente, los derivados de β -ciclodextrina anteriormente mencionados, cuando están asociados a un tampón apropiado, por ejemplo un tampón fosfato, en las composiciones de la invención, permiten aumentar específicamente la solubilidad acuosa de la dronedarona o de sus sales farmacéuticamente aceptables. En el caso, por ejemplo, del clorhidrato de dronedarona, la

solubilidad puede ser aumentada en esas condiciones hasta alrededor de 6,5 mg/ml en presencia de un tampón fosfato 100 mmolar y de 5% de hidroxipropil β -ciclodextrina.

Además, los derivados de β -ciclodextrina, en particular la hidroxipropil β -ciclodextrina, se han revelado aptos para prevenir la auto-asociación de las moléculas de dronedarona o de sus sales farmacéuticamente aceptables, por formación de un complejo de encapsulación de ese principio activo. Ese complejo de encapsulación molecular se ha revelado seguidamente capaz de atravesar la membrana celular manteniéndola intacta y, por consiguiente, de poner remedio a los problemas de intolerancia local puestos en evidencia con composiciones que contienen ya sea un tampón apropiado o un derivado de β -ciclodextrina.

Si es necesario, las composiciones de la invención pueden comprender uno o varios ingredientes complementarios especialmente un agente conservante o protector tal como un bactericida o un compuesto que permita mantener la isotonicidad de la composición tal como el manitol.

Las composiciones de la invención así formadas, se caracterizan por una estabilidad importante que permite conservarlas de manera durable y a la vez utilizarlas eficazmente para una administración por inyección.

Las composiciones farmacéuticas de la invención pueden ser obtenidas de manera clásica calentando a una temperatura

78
75

de 50°C a 60°C, preferentemente a 55°C, un medio acuoso formado del sistema tampón apropiado, del derivado soluble de β -ciclodextrina y de eventuales excipientes complementarios, introduciendo posteriormente, a esta temperatura, el principio activo.

Las características y ventajas de las composiciones de acuerdo con la invención se verán a la luz de la descripción que sigue a partir de composiciones dadas a título de ejemplos.

I. Tolerancia local en el animal

Se han practicado tests para evaluar la tolerancia local de diferentes composiciones acuosas conteniendo el clorhidrato de dronedarona o únicamente el vehículo correspondiente como placebo.

A este efecto, se ha administrado diariamente, por vía endovenosa a lotes de 5 ratas machos durante 5 días, una dosis de una de las composiciones acuosas más abajo descritas. Se ha practicado la inyección en la vena caudal, de preferencia, en zona distal, luego en zona mediana y finalmente en zona proximal.

Entonces se sacrificaron los animales al 8° día y se les sacaron las colas para un eventual examen microscópico.

Se obtuvieron los siguientes resultados:

a) Composiciones con 0,1% de dronedarona base

. Dosis administrada: 5 ml/kg o sea 5 mg/kg/día

79
76

. Composiciones testeadas

INGREDIENTES	COMPOSICIÓN (en mg)					
	A	B	C	D	E	F
Clorhidrato de dronedarona (correspondiente a 1mg de dronedarona base)	1,065	-	1,065	-	1,065	-
Hidroxiopropil. β - ciclodextrina	50	50	50	50	-	-
Fosfato monosódico anhidro	12	12	-	-	12	12
Manitol apirógeno	8	8	45	45	20	20

Estos ingredientes se agregan con cantidad suficiente de agua para obtener un volumen de 1 ml.

Las composiciones A, B, E y F tienen un pH de 4,5 y las composiciones C y D, un pH comprendido entre 4,5 y 6,5.

1) Composición A (o composición que contiene un derivado de β -ciclodextrina y un tampón fosfato)

No se ha notado ningún signo clínico local.

La tolerancia local de esta formulación puede ser considerada como muy buena.

2) Composiciones B, D y F (o composiciones placebo)

No se ha registrado ningún signo clínico local.

3) Composición C (o composición que contiene un derivado de β -ciclodextrina pero sin tampón fosfato)

Después de una única inyección, la cola de todos los animales presentaba manchas rojas locales y tenía una consistencia dura. A partir de la segunda inyección, las siguientes fueron dolorosas y debieron ser efectuadas en el segmento medio luego proximal (base) de la cola.

Teniendo en cuenta el estado de la cola, no fue posible poner inyecciones a continuación. Así, 2 animales sólo pudieron recibir 3 inyecciones, otros 2 sólo recibieron 4 mientras que uno sólo pudo ser tratado durante los 5 días. Al 5° día, las colas de 4 animales aparecían negras (necrosis probable).

La intolerancia local de esta composición es considerada como severa.

4) Composición E (o composición que contiene un tampón fosfato pero sin derivado de β -ciclodextrina).

Después de 1 o 3 inyecciones, la cola de los animales presentaba manchas rojas locales sobre toda la extensión. Al 4° día, 2 animales debieron recibir la inyección en el segmento medio (y no más distal). Al 5° día, las dificultades técnicas debidas al mal estado de las colas impidieron el tratamiento de 4 animales y la cola de todos los animales tenía una consistencia dura.

Se considera la intolerancia local de esta formulación

87
78

como acentuada.

En conclusión, la totalidad de estos resultados muestra claramente que entre las composiciones que contienen el clorhidrato de dronedarona, sólo la formulación que recurrió a la vez a un tampón y a un derivado de β -ciclodextrina mostró una tolerancia local satisfactoria.

b) Composiciones con 0,4% de dronedarona base

- . Dosis administrada: 2 ml/kg o sea 2 mg/kg/día
- . Composiciones testeadas

INGREDIENTES	COMPOSICIÓN (en mg)			
	G	H	I	J
Clorhidrato de dronedarona (correspondiente a 4 mg de dronedarona base)	4,260	-	4,260	-
Hidroxipropil. β -ciclodextrina	50	50	-	-
Mezcla de derivados metilados de β -ciclodextrina	-	-	50	50
Fosfato monosódico anhidro	12	12	12	12
Manitol apirógeno	8	8	8	8

Estos ingredientes se agregan con cantidad suficiente de agua para obtener un volumen de 1 ml.

Las cuatro composiciones tienen un pH de 4,5.

1) Composiciones G e I (o composiciones que contienen un

derivado de β -ciclodextrina y un tampón fosfato)

No se ha notado ningún signo clínico local.

2) Composiciones H y J (o composiciones placebo)

No se ha registrado ningún signo clínico local.

La tolerancia local de estas formulaciones puede ser considerada como muy buena y equivalente.

Estos resultados muestran de nuevo la excelente tolerancia local de las composiciones que contienen el clorhidrato de dronedarona cuando incluyen a la vez un tampón apropiado y un derivado de β -ciclodextrina.

II. Tolerancia local en el hombre

Se han practicado tests comparativos para evaluar la tolerancia local de dos formulaciones de clorhidrato de dronedarona, una conteniendo un tampón fosfato pero sin derivado de β -ciclodextrina en este caso la Composición E, otra incluyendo los dos compuestos a saber:

INGREDIENTES	COMPOSICIÓN K (en mg)
Clorhidrato de dronedarona (correspondiente a 4 mg de dronedarona base)	4,26
Manitol apirogeno	8,0
Hidroxipropil- β -ciclodextrina	50,0
Fosfato monosódico dihidratado	15,6

Estos ingredientes fueron agregados con la cantidad suficiente de agua para obtener un volumen de 1 ml.

A) En una primera serie de pruebas, se utilizaron 28 personas sanas de sexo masculino distribuidas en 7 grupos de 4 personas:

. 3 personas de cada grupo recibieron, a partir de la Composición E administrada por perfusión en la vena antecubital, una dosis de clorhidrato de dronedarona correspondiente a 5, 10, 20 o 40 mg de dronedarona base en 30 minutos o una dosis de clorhidrato de dronedarona correspondiente a 40, 60 u 80 mg de dronedarona base en 60 minutos, 1 persona por grupo recibió el placebo igualmente por perfusión.

Esta Composición E fue utilizada luego de dilución en una solución de 5% con dextrosa de manera de obtener para cada una de las pruebas, una concentración de principio activo de 0,333 mg/ml. Por consiguiente, para cada dosis testeada, cambió el volumen de perfusión y la velocidad de administración por minuto.

A continuación de estas perfusiones, 2 personas que habían recibido su dosis en 30 minutos presentaron una flebitis que ha desaparecido, persistiendo un endurecimiento de la vena siempre presente después de 8 días.

Asimismo, 3 personas que habían recibido su dosis en 60 minutos presentaron una inflamación venosa. La misma

desapareció pero dejó un endurecimiento de la vena todavía presente después de 8 días.

Ninguna de las personas que había recibido el placebo ha manifestado reacción en el sitio de perfusión.

B) En una segunda serie de tests, se han utilizado 32 personas sanas de sexo masculino distribuidas en 5 grupos:

. 3 personas de 2 grupos recibieron, a partir de la Composición K administrada por perfusión en la vena antecubital, una dosis de clorhidrato de dronedarona correspondiente a 10 o 20 mg de dronedarona base y en 30 minutos, 1 persona por grupo recibió el placebo igualmente por perfusión.

. 6 personas de 3 grupos recibieron, a partir de la Composición K administrada por perfusión en la vena antecubital, una dosis de clorhidrato de dronedarona correspondiente a 40, 60 u 80 mg de dronedarona base y en 30 minutos, 2 personas por grupo recibieron el placebo igualmente por perfusión.

Esta Composición K fue utilizada luego de dilución en una solución de 5% de dextrosa. Además, se fijó el volumen de perfusión a 120 ml y la velocidad de administración a 4 ml/minuto.

Por consiguiente, la concentración en clorhidrato de dronedarona aumentó en el líquido de perfusión de acuerdo con la dosis de principio activo a administrar pasando de 0,083

82
85

mg/ml para una dosis de 10 mg a 0,666 mg/ml para una dosis de 80 mg.

A continuación de estas perfusiones, la tolerancia local parece mejor que con la Composición E porque no se registró ninguna flebitis ni inflamación venosa en cada una de las dosis testeadas.

En comparación con la Composición E, los resultados registrados con la Composición K son particularmente notables a las dosis de 40, 60 y 80 mg ya que el período de perfusión fue más corto (30 minutos en lugar de 60 minutos para la Composición E) y la concentración del líquido de perfusión administrado más elevada.

En efecto, a la dosis de 80 mg, la concentración de clorhidrato de dronedarona en la Composición K perfusada era de 0,666 mg/ml en lugar de 0,333 mg/ml que es el caso de la Composición E.

Estos resultados confirman, en el ser humano, la muy buena tolerancia de las composiciones que contienen el clorhidrato de dronedarona, un tampón apropiado y un derivado de β -ciclodextrina con relación a las composiciones análogas desprovistas de un tampón.

Los ejemplos no limitativos siguientes ilustran la invención.

EJEMPLO 1

Composición inyectable de clorhidrato de dronedarona

Se preparó una composición farmacéutica inyectable que responde a la siguiente formulación:

Clorhidrato de dronedarona (correspondiente a 4 mg de dronedarona base)	4,26 mg
Hidroxipropil β -ciclodextrina	50,00 mg
Fosfato monosódico dihidratado	15,60 mg
Manitol	8,00 mg
Agua	cantidad suficiente para 1 ml

(para preparación inyectable) por aplicación del procedimiento descrito a continuación.

Se solubilizan 50 mg de hidroxipropil β -ciclodextrina, 15,6 mg de fosfato monosódico dihidratado y 8 mg de manitol en 75% del agua para preparación inyectable total. Se calienta a 55° C la solución obtenida, luego, bajo agitación magnética, se introducen 4,26 mg de clorhidrato de dronedarona. Se prosigue la agitación magnética durante 30 minutos, luego se completa la solución hasta 100 % del volumen final con el agua para preparación inyectable. Se filtra la solución de clorhidrato de dronedarona sobre membrana de porosidad 0,22 μ m y se verifica la limpidez de esta solución, el pH y la osmolalidad.

Se obtuvieron los siguientes resultados:

Turbidez: 1,1 NTU (unidad de turbidez nefelométrica)

pH: 4,5

Osmolalidad: 311 mosmol./kg

87
84

La solución así obtenida es límpida e isotónica. Puede ser llevada en autoclave a 121°C durante 35 minutos. Es estable durante 6 meses a 5°C, 25°C y 40°C y diluible en solución al 5% de glucosa y 0,9% de cloruro de sodio.

EJEMPLOS 2 a 4

Siguiendo el mismo método que en el Ejemplo 1, se prepararon las siguientes composiciones:

Ej. 2	Clorhidrato de dronedarona (correspondiente a 4 mg de dronedarona base)	4,26 mg
	Hidroxipropil β -ciclodextrina	50,00 mg
	Fosfato monosódico anhidro	12,00 mg
	Manitol	8,00 mg
	Agua	cantidad suficiente para 1 ml
	(para preparación inyectable)	
Ej. 3	Clorhidrato de dronedarona (correspondiente a 1 mg de dronedarona base)	1,065 mg
	Hidroxipropil β -ciclodextrina	50,00 mg
	Fosfato monosódico anhidro	12,00 mg
	Manitol	8,00 mg
	Agua	cantidad suficiente para 1 ml
	(para preparación inyectable)	
Ej. 4	Clorhidrato de dronedarona (correspondiente a 4 mg de dronedarona base)	4,26 mg
	Mezcla de derivados metilados de β -ciclodextrina	50,00 mg

88
45

20

Manitol	8,00 mg
Agua	cantidad suficiente para 1 ml
(para preparación inyectable)	

EJEMPLO 5

Unidad de dosificación para administración inyectable de
clorhidrato de dronedarona

Se esteriliza en autoclave a 121°C durante 35 minutos, una ampolla de vidrio de un volumen total de 3 ml conteniendo 1 ml de una composición de clorhidrato de dronedarona tal como se preparara en el Ejemplo 1.

Se sella entonces la ampolla bajo asepsia de manera de constituir una unidad de dosificación conteniendo 4,26 mg de clorhidrato de dronedarona equivalente a 0,4 % de dronedarona base.

89
86

REIVINDICACIONES

1. Composición farmacéutica para administración parenteral, caracterizada porque comprende:

- . la dronedarona o una de sus sales farmacéuticamente aceptables como principio activo,
- . una solución tampón fisiológicamente aceptable capaz de mantener el pH de la composición entre 3 y 5,
- . un derivado hidrosoluble de β -ciclodextrina fisiológicamente aceptable.

2. Composición farmacéutica de acuerdo con la reivindicación 1, caracterizada porque contiene entre 0,01% y 4% de principio activo.

3. Composición farmacéutica de acuerdo con la reivindicación 2, caracterizada porque contiene entre 0,4% y 0,8% de principio activo.

4. Composición farmacéutica de acuerdo con una de las reivindicaciones 1 a 3, caracterizada porque la solución tampón es una solución acuosa que contiene un sistema tampón seleccionado entre los siguientes:

- . ácido acético/acetato de metal alcalino
- . ácido fumárico/fumarato de metal alcalino
- . ácido succínico/succinato de metal alcalino
- . ácido cítrico/citrato de metal alcalino
- . ácido tártrico/tartrato de metal alcalino
- . ácido láctico/lactato de metal alcalino

- . ácido maleico/maleato de metal alcalino
- . ácido metansulfónico/metansulfonato de metal alcalino
- . fosfato monometálico alcalino

5. Composición farmacéutica de acuerdo con la reivindicación 4, caracterizada porque el sistema tampón es un fosfato monometálico alcalino.

6. Composición farmacéutica de acuerdo con la reivindicación 4, caracterizada porque la solución tampón de fosfato monometálico alcalino mantiene el pH en 4,5.

7. Composición farmacéutica de acuerdo con una de las reivindicaciones 1 a 6, caracterizada porque la fuerza iónica de la solución tampón está comprendida entre 0,005 molar y 0,5 molar.

8. Composición farmacéutica de acuerdo con la reivindicación 7, caracterizada porque la fuerza iónica de la solución tampón está comprendida entre 0,01 molar y 0,2 molar.

9. Composición farmacéutica de acuerdo con la reivindicación 7 u 8, caracterizada porque la fuerza iónica de la solución tampón está comprendida entre 0,05 y 0,15 molar.

10. Composición farmacéutica de acuerdo con las reivindicaciones 1 a 9, caracterizada porque la solución tampón es una solución acuosa 0,05 molar a 0,15 molar en fosfato monometálico alcalino.

11. Composición farmacéutica de acuerdo con la reivindicación 4, 5, 6 o 10, caracterizada porque el metal alcalino es sodio o potasio.

12. Composición farmacéutica de acuerdo con una de las reivindicaciones 1 a 11, caracterizada porque el derivado hidrosoluble de β -ciclodextrina se selecciona entre la hidroxipropil β -ciclodextrina, el derivado sulfobutil éter de β -ciclodextrina, la dimetil β -ciclodextrina, la trimetil β -ciclodextrina así como sus mezclas.

13. Composición farmacéutica de acuerdo con una de las reivindicaciones 1 a 12, caracterizada porque el derivado hidrosoluble de β -ciclodextrina es la hidroxipropil β -ciclodextrina.

14. Composición farmacéutica de acuerdo con una de las reivindicaciones 1 a 13, caracterizada porque el derivado hidrosoluble de β -ciclodextrina está presente a razón de 0,5 a 50%.

15. Composición farmacéutica de acuerdo con una de las reivindicaciones 1 a 14, caracterizada porque el derivado hidrosoluble de β -ciclodextrina está presente a razón de 5 a 20 veces el peso de dronedarona o de una de sus sales farmacéuticamente aceptables.

16. Composición farmacéutica de acuerdo con la reivindicación 15, caracterizada porque el derivado hidrosoluble de β -ciclodextrina está presente a razón de 12

92
89

a 13 veces el peso de dronedarona o de una de sus sales farmacéuticamente aceptables.

17. Composición farmacéutica de acuerdo con una de las reivindicaciones 1 a 16, caracterizada porque contiene además un agente conservador o protector.

18. Composición farmacéutica de acuerdo con una de las reivindicaciones 1 a 17, caracterizada porque contiene además un compuesto que permite mantener la isotonicidad.

19. Composición farmacéutica de acuerdo con una de las reivindicaciones 1 a 18, caracterizada porque el principio activo es el clorhidrato de dronedarona.

TRADUCCIÓN OFICIAL No.311/03 DE UN DOCUMENTO ESCRITO EN FRANCÉS, EL CUAL PARA SU IDENTIFICACIÓN SE SELLA CON EL SELLO DEL TRADUCTOR. ESTA ES UNA TRADUCCIÓN OFICIAL EFECTUADA EL DIA 16 DE MAYO DEL AÑO 2003 POR JEAN-JACQUES TURPIN, C.E.: 193849 DE BOGOTÁ, TRADUCTOR E INTÉRPRETE OFICIAL SEGÚN RESOLUCIÓN No. 2680/91 DEL 19 DE DICIEMBRE DE 1991, EXPEDIDA POR EL MINISTERIO DE JUSTICIA DE COLOMBIA.

Autenticaciones que se hallan a continuación de un documento de cesión conferido en inglés y español por **BOURRIAGUE-SEVE Frédérique** y **BREUL Thierry**, domiciliados respectivamente en Le Village, FR-34190 FERRIERES LES VERRERIES, y 118, avenue F. De Lesseps, FR-34110 FRONTIGNAN, quienes declaran bajo juramento ser los únicos y verdaderos inventores de :*"COMPOSICIÓN FARMACÉUTICA DE DRONEDARONA PARA ADMINISTRACIÓN PARENTERAL"*. Asimismo, declaran ceder a **SANOFI-SYNTHELABO**, una compañía organizada y existe bajo las leyes de Francia, domiciliada en 174, avenue de France, 75013 PARIS, FRANCIA, todos sus derechos inherentes a dicha invención y que la citada sociedad queda facultada para solicitar en su nombre la patente correspondiente en la República de Colombia.

Dado el 25 de abril de 2003. Firma ilegible de los Señores **BOURRIAGUE-SEVE Frédérique** y **BREUL Thierry**.

Legalización de la firma de los Señores **BOURRIAGUE-SEVE Frédérique** y **BREUL Thierry** por **Alain KOENIG**, Notario en Paris. Dado en Paris, el 29 de abril de 2003.
Firma ilegible del Notario.

Sello: Alain Koenig – Notario – 20, rue de la Paix – 75004 Paris Cedex 02.

Sello seco: Alain Koenig - Notario en Paris – Tribunal Superior – República Francesa.

94
91

APOSTILLA
(Convención de La Haya del 5 de octubre de 1961)

1. - República Francesa

El presente documento público

2. - ha sido firmado por el Doctor Koenig

3. - obrando en calidad de Notario

4. - con sello de su Notaria

CERTIFICADO

5. - En Paris

6. - El 05 de mayo de 2003

7. - Por el Procurador General ante el Tribunal Superior

8. - Bajo el número 41389/2003

9. - Sello: Tribunal Superior de Paris – Procurador General - República Francesa.

10. - Firma ilegible.

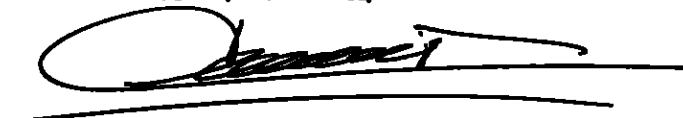
Es traducción fiel y completa de la cual se deja copia en los archivos de esta oficina para confrontación y a la cual me remito.

Traducción oficial No. 311/03.

Traductor: Jean-Jacques Turpin.

Bogotá, D.C., 16 de mayo de 2003.

Traducción Oficial No. 311/03
JEAN - JACQUES H. TURPIN
Traductor e Intérprete Oficial
FRANCOIS - ESPANOL
Reg. Minjusticia No. 2480/91



MINISTERIO DE RELACIONES
EXTERIORES

Enman Thompson

029489

CUYA FIRMA APARECE EN EL
DOCUMENTO DESEMPEÑA
LAS FUNCIONES DE

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

2003 MAY 20 P 12:40

JEFE DE LA FUERZA ARMADA
SANTA FE DE BOGOTÁ

ASSIGNMENT

The undersigned

- 1) BOURRIAGUE-SEVE Frédérique
- 2) BREUL Thierry

domiciled in

- 1) Le Village, FR-34190 FERRIERES LES VERRERIES
- 2) 118 avenue F. de Lesseps, FR-34110 FRONTIGNAN

hereby state under oath to be the sole and true inventor of

PHARMACEUTICAL DRONEDARONE COMPOSITION FOR PARENTERAL ADMINISTRATION

state as well that they assign without reservation or limitation, in favor of
SANOFI-SYNTHELABO and ,

a corporation organized and existing under the laws of
France

domiciled in
174, Avenue de France
75013 PARIS
FRANCE

all rights inherent to said invention, and that the above mentioned corporation hereby is enabled to apply, in its name, for the corresponding patent in the Republic of Colombia

TRAPASO

Abajo firmado

- 1) BOURRIAGUE-SEVE Frédérique
- 2) BREUL Thierry

Domiciliado en

- 1) Le Village, FR-34190 FERRIERES LES VERRERIES
- 2) 118 avenue de F. de Lesseps, FR-34110 FRONTIGNAN

Decla bajo juramento ser unico y verdadero inventor de

COMPOSICION FARMACEUTICA DE DRONEDARONA PARA ADMINISTRACION PARENTERAL

Declar asimismo que ced y transf sin reserva ni limitacion, a favor de la sociedad

SANOFI-SYNTHELABO y,
una sociedad

Organizada y existente de conformidad con las leyes de
Francia

Domiciliada en
174 Avenue de France
75013 PARIS
FRANCIA

Todos los derechos inherentes a dicha invencion y que la citatda sociedad queda facultada para solicitar en su nombre la patente correspondiente en la Republica de Colombia

25 AVR. 2003

- 1) BOURRIAGUE-SEVE Frédérique

- 2) BREUL Thierry



Vu pour certification
matérielle de la signature
de M. BOURRIAGUE-SEVE
N. BREUL
apposée d.
PARIS, le 29/04/03.

APOSTILLE

(Convention de la Haye du 5 Octobre 1961)

— République Française

Le présent acte public

— a été signé par Me Koenig

— agissant en qualité de Notaire

est revêtu du sceau de la Cour



ATTESTE - 5 MAI 2003

le

— Par le Procureur Général près la Cour d'appel

Sous N° 41989 (2003)

— Sceau De signature

[Signature]

REQUISITOS MINIMOS PARA ADMISION A TRAMITE

PCT

PATENTE DE INVENCION ☒

MODELO DE UTILIDAD ☐

- Indicacion de que se solicita la concesion de una patente
- Datos de identificacion del solicitante o de la persona que presenta la solicitud
- Descripcion de la invencion
- Dibujos de ser estos pertinentes
- Comprobante de Pago de las tasas establecidas

111
111
169
11
1243

COMPLETA ☒

INCOMPLETA ☐

DISEÑO INDUSTRIAL ☐

- Indicacion de que se solicita el registro de Diseño Industrial.
- Datos de identificacion del solicitante o de la persona que presenta la solicitud.
- Representacion grafica y fotografica del Diseño Industrial o muestra del material que incorpora el diseño.
- Comprobante de pago de las tasas establecidas.

[]
[]
[]
[]

COMPLETA ☐

INCOMPLETA ☐

ESQUEMA DE TRAZADO ☐

- Indicacion de que se solicita el registro de un Esquema de trazado.
- Datos de identificacion del solicitante o de la persona que presenta la solicitud.
- Representacion grafica del esquema de trazado
- Comprobante de pago de las tasas establecidas.

[]
[]
[]
[]

COMPLETA ☐

INCOMPLETA ☐

Firma Responsable

Fecha: _____



Folio 91

2020
Bogotá DC

Doctor(a)
JOSE ANTONIO LLOREDA
Apoderado(a)

REFERENCIA:	Radicación No.	03-48164
	Solicitud Internacional	PCT/FR2001/03903
	Fecha inicio fase nacional	11/07/2003
	Trámite	011
	Evento	379
	Actuación	416
	Oficio No.	1172
	Folios	001

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Unica de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial.

Cúmplase
Dado en Bogotá DC,

22 SET. 2003


ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

202060