



Industria y Comercio

SUPERINTENDENCIA

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Handwritten: PCT

**SOLICITUD
PATENTE DE INVENCION**

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21. **EXPEDIENTE No.**

54. **TITULO**

USO DE BIEN4096 EN COMBINACION CON OTROS FARMACOS
ANTIMIGRANOSOS PARA EL TRATAMIENTO DE LA MIGRAÑA

51. **CLASIFICACION INTERNACIONAL**

Handwritten: A61K31/517

71. **SOLICITANTE**

BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG.

DOMICILIO

Ingelheim am Rhein, República Federal de Alemania.

74. **APODERADO**

EMILIO FERRERO

Código No. 1092

22. **SANTAFE DE BOGOTA, D.C.**

Handwritten: 10/10/09

Handwritten signatures and marks



Industria y Comercio
SUPERINTENDENCIA



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SUPERINDUSTRIA Y COMERCIO

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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO UNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

SOLICITUD DE:

1

☒ Patente de Invención.

☐ Patente de Modelo de Utilidad.

☐ Capítulo I.

☒ Capítulo II.

2

SOLICITANTE
(71)

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

Dirección: **Binger Strasse 173,
55216 Ingelheim am Rhein,
República Federal de Alemania**

Domicilio: **Ingelheim am Rhein,
República Federal de Alemania**

IDENTIFICACIÓN

C.C. ☐ NIT ☐

C.E. ☐ Otro ☐

Cual _____

Número _____

3

**REPRESENTANTE
O APODERADO**

Nombre: **EMILIO FERRERO**
Dirección: **Carrera 4ª. No. 72-35**
Teléfono: **347 38 11**
Fax: **217 92 11**
E-mail: **clientes@camyp.com.**
Domicilio: **Bogotá, Colombia.**

IDENTIFICACIÓN

C.C. ☒ NIT ☐

C.E. ☐ Otro ☐

Cual _____

Número **438.019** T.P **31.929**

4

INVENTOR (ES)
(72)

1. **Henri DOODS**
Freiherr-von-König-Straße 6
88447 Warthausen
República Federal de Alemania

3. **Wolfgang EBERLEIN**
Obere Au 6
88400 Biberach
República Federal de Alemania

2. **Klaus RUDOLF**
Öschweg 11
88447 Warthausen
República Federal de Alemania

5

PCT (86)

Solicitud Internacional No. **PCT/EP02/08993**

Fecha: **10 de Agosto de 2002**

Publicación Internacional No. **WO 03/015787 A1**

Fecha : **27 de Febrero de 2003**

6

Título (54)

**USO DE BIBN4096 EN COMBINACIÓN CON OTROS FÁRMACOS
ANTIMIGRAÑOSOS PARA EL TRATAMIENTO DE LA MIGRAÑA**

7

Clasificación Internacional (51) A61K 31/517

8

Prioridad

SI ☒ NO ☐

(33) País de Origen

DE

(32) Fecha

17 de Agosto de 2001

(31) Número de Solicitud

101 39 410.1

9

Comprobante de pago No.: 04 - 8.090

Fecha: Febrero 2 de 2004

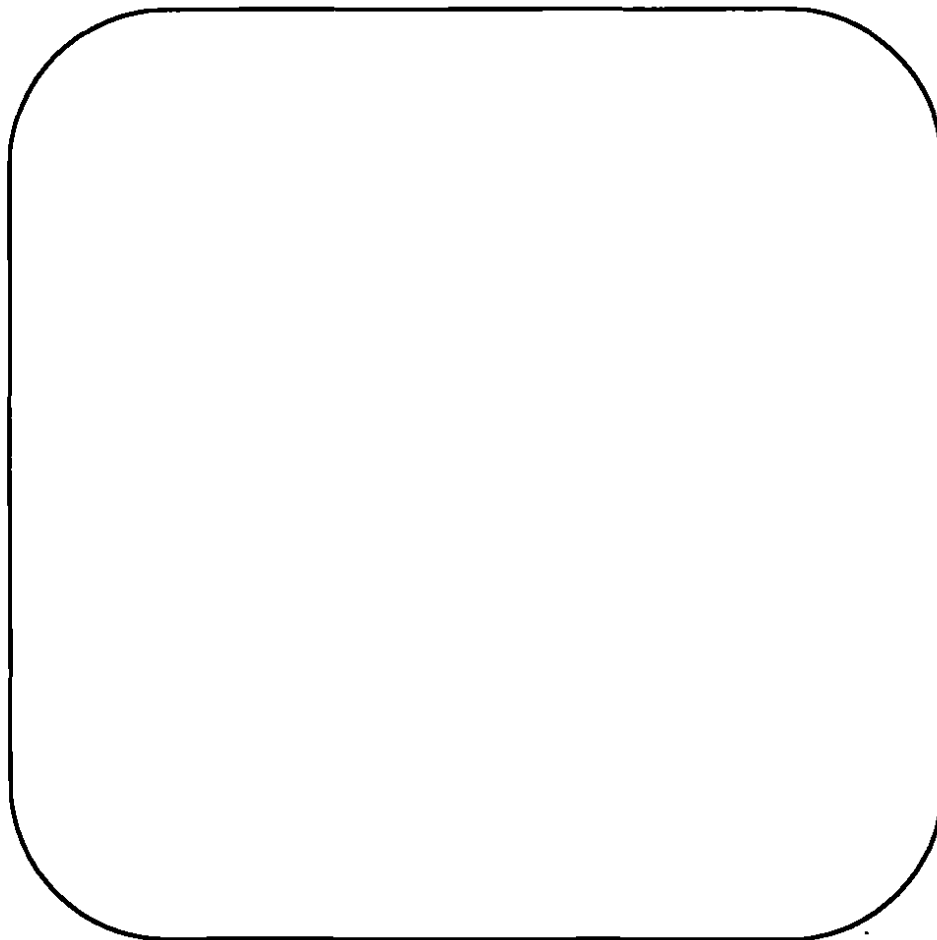
32

10

Anexos:

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por \$ 422.000.00.
- ☐ Comprobante de pago por reivindicación de prioridad.
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso.
- ☐ 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, dibujos)
- ☒ Copia del examen preliminar efectuado por la IPEA.
- ☒ Traducción del examen preliminar 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.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☐ Arte final 12x12
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☒ Otros: FORMA PCT/IB/306 NOTIFICACIÓN DEL REGISTRO DE UN CAMBIO (NOTIFICATION OF THE RECORDING OF A CHANGE) – CAMBIO DE NOMBRE DEL SOLICITANTE

11

FIGURA CARACTERÍSTICA

12

Solicito la concesión de la patente,

NOMBRE: EMILIO FERREROFIRMA: 

C.C. 438.019 de Usaquén T.P. 31.929

PRP

Representación y Poder con autenticación notarial y Apostille para patentes, modelos de utilidad, diseños industriales, marcas de fábrica, nombres comerciales, enseñas, nombres de dominio, lemas comerciales, licencias.

Representation and Power-of- Attorney with notarial authentication and Apostille for patents, utility models, industrial designs, trademarks, commercial names, trade emblems, domain names, slogans, licenses.

REPRESENTACION Y PODER

REPRESENTATION AND POWER- OF- ATTORNEY

Yo (nosotros), abajo firmado (s)/I (we), the undersigned
BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG

13736
0564

domiciliado (s) en/of
55216 Ingelheim, Germany

por el presente nombramos a EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 y GERMAN CAVELIER, tpa. 832, domiciliados en la Carrera 4ª N° 72 35, Bogotá, Colombia, en obediencia a lo dispuesto en el párrafo 1o del Artículo 543 del Código de Comercio, el primero como principal y los demás como suplentes, en su orden, como mis (nuestros) representantes en todos los asuntos de propiedad industrial con facultad para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales. El primer representante suplente reemplazará al principal en caso de ausencia o impedimento temporal o definitivo de aquél. La misma regla se aplicará cuando el segundo representante suplente haya de reemplazar al primero, o el tercero al segundo. En tales casos, el representante principal, o el primero, o segundo suplente, en su caso, o ambos, declararán su intención de no ejercer la representación mediante declaración autenticada por Notario Público en Colombia, o por Notario u otro Funcionario Público, o Cónsul de Colombia, en el extranjero; y si se tratare de impedimento, con el certificado respectivo. Si alguno de los nombrados faltare definitivamente, el siguiente tomará su lugar. Cuando cesare la ausencia o impedimento del representante principal, o de su primero o segundo suplentes, en su caso, podrán ejercer la representación, en su orden, uno u otros según el caso, asumiéndola por el solo hecho de ejercerla, cesando en ese momento el ejercicio de la representación por el primero, segundo o tercer suplente en su caso.

Además, confiero (conferimos) poder a los abogados arriba nombrados, para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera entidades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos de utilidad, y diseños industriales; el registro de marcas de fábrica, colectivas, defensivas, de servicio, lemas comerciales, nombres comerciales, enseñas, nombres de dominio, variedades vegetales y denominaciones de origen; su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) Las acciones de competencia desleal, protección del consumidor, oposiciones u observaciones, cancelación administrativa y judicial, nulidad, medidas cautelares, concesión de licencias, la tutela, la protección de secretos industriales, y en general los juicios civiles, penales, administrativos o contencioso administrativos relacionados con estos derechos; acciones y procesos que promovamos o se nos

in due compliance with the terms of paragraph 1st. of article 543 of the Commercial Code, do hereby appoint EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 and GERMAN CAVELIER, tpa. 832, domiciled at Carrera 4ª N° 72 35, Bogotá, Colombia, the first as principal and the others as alternates, in the order of their appointment, as our representatives for all industrial property matters with faculty to receive notifications and to appoint attorneys in and out of Court. The first alternate shall replace the principal in case of his absence or of temporal or definitive impediment. The same rule will apply when the second alternate representative is to replace the first one, or when the third is to replace the first or second alternates in their turn, or both of them, second. In such cases, the principal representative, or the first or second alternates in their turn, or both of them, shall state their intention not to act as representatives through a declaration given before a Notary Public in Colombia, or before a Notary or another Public Official or a Colombian Consul abroad; and in case of impediment, the appropriate certificate shall suffice. If any of the appointees were to be definitely absent, the following alternate shall take his place. When the absence or impediment of the principal representative, or of the first or second alternate in their turn ceases, the representation can be taken again in their sequence, by the principal, the first or second alternate depending on the order of their appointment, or its exercise will suffice. The exercise of the representation, by the first, second or third alternates in their turn, shall end at such time.

12 FEB 2004

In addition, we grant a Power of Attorney in favor of the above named attorneys at law so that they may obtain the protection of my (our) industrial property and against the unfair competition, for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, specially those administrative, administrative contentious and judicial, as well as before Arbitration Court, in all matters concerning the following: a) Obtainment of patents, utility models and industrial designs; the registration of trademarks, collective, defensive and service marks, slogans, commercial names, trade emblems, domain names, vegetal varieties and denominations of origin; its renewal, assignment, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rights; b) Actions of unfair competition, protection to the consumer, oppositions or observations, administrative or Court cancellation, nullity, infringement, granting of licenses, the action for writ mandamus, the protection of trade secrets, and in general the civil, penal, and administrative suits relating to those rights; actions and suits instituted by me (us) or against me (us). And that in all the above matters they may substitute this Power of Attorney, compromise, conciliate,

admit the facts of the case, desist, cancel, receive, resign, and not done by representatives without a power of attorney.

por/by _____

Signature

ppa

ppa

Dr. Michael KOMPTER
Principal Officer



AUTENTICACION NOTARIAL (SOCIEDAD)

El infrascrito Notario Certifica: Que la firma que antecede de

1. Heinz-Gerd Kläs y
 2. Michael Kompter
 es auténtica; que el signatario desempeña actualmente el cargo
 de Representante
 de la compañía Boehringer Ingelheim Pharma
GmbH & Co. KG
 sociedad que actualmente existe y está organizada de acuerdo a
 las leyes de Alemania

que la dirección de la compañía es 55216 Ingelheim
am Rhein Binger Straße 173

y que el signatario tiene facultad para otorgar este documento.

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

Dado y firmado en Ingelheim am Rhein

21 Marzo 2003

NOTARIAL AUTHENTICATION (COMPANY)

The undersigned Notary certifies: That the preceding signature
 of 1.Mr.Dr.Heinz-Gerd Kläs and
 2.Mr.Dr.Michael Kompter

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

of the company Boehringer Ingelheim Pharma
GmbH & Co. KG

a company currently existing and organized under the laws of
Germany

that the address is 55216 Ingelheim am Rhein
Binger Straße 173

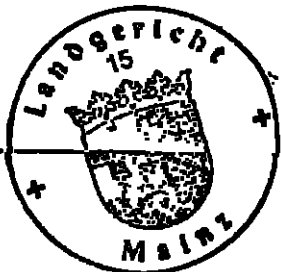
and that the signatory has the power to grant this document.

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

Given and signed in Ingelheim am Rhein

On the 21th day of March 2003

Notary Public
 (Signature-seal)



Apostille

(Convention de La Haye du 5 octobre 1961)

1. Land Bundesrepublik Deutschland

Diese öffentliche Urkunde

2. ist unterschrieben von

Alfred Fuchs

3. in seiner Eigenschaft als Notar

4. sie ist versehen mit dem Dienstsiegel
 des Alfred Fuchs - Notar in Ingelheim am Rhein

Bestätigt

Mainz, den 24.03.03

5. in Mainz 6. am 24.03.03

7. durch den Präsidenten des Landgerichts

8. unter Nr. 269/2003

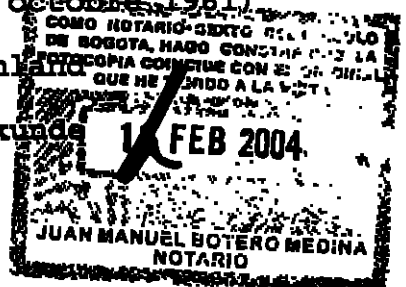
9. Stempel/Siegel 10. Unterschrift

In Vertretung:

Justizsekretärin



Dr. Harald Bing
 (Dr. Harald Bing)
 Vizepräsident



KOSTENRECHNUNG:

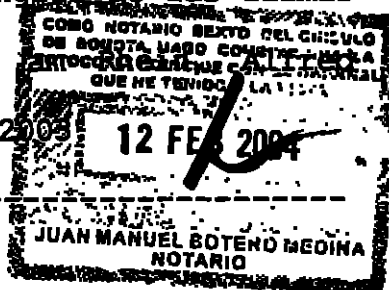
Gebühr für die
 Erteilung der
 Legalisation
 Wert: EUR 20.000,00
 JVKostO v.26.7.57
 i.V.m. § 45 KostO
 Gebühr: EUR 18,00

TRADUCCION OFICIAL No. 9468

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

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

Sigue autenticación notarial en español e inglés de las firmas antecedentes por el notario de Ingelheim Fuchs, el 21 de marzo 2003, bajo el No. 571/2003



COSTAS:

Derechos de legalización

Valor: EUROS 20.000,--

LUZ ARRIAGA DE HERBER
TRADUCCION OFICIAL
Resolución No. 599 del 6 de marzo 1978

JVKostO del 26.7.57 en combinación con Art. 45 KostO

Derechos: EUROS 18,00

Mainz, 24.03.03

Fdo.: ilegible,

Secretaria de justicia

APOSTILLA

(Convention de La Haye du 5 octobre 1961)

1. País: República Federal de Alemania

Este documento público

2. Ha sido firmado por el notario Alfred Fuchs

3. Actuando en calidad de notario

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

Certificado

5. en Mainz

6. el 24.03.03

7. por el Presidente del Tribunal Regional

8. bajo el No 269/2003 /

9. Sello

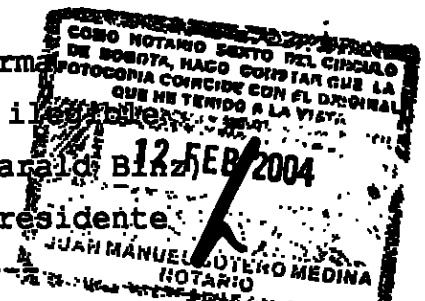
Tribunal Regional de Mainz

10. Firma

Fdo.: ilegible

(Dr. Harald Binz)

Vicepresidente



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

Bogotá, 7 de abril 2003

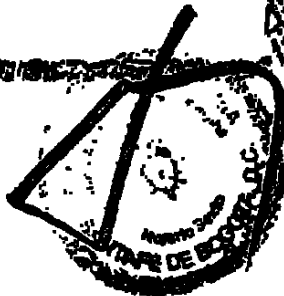
LUZ ANTONIO DE HERBER
EXDUCO EN EL NOMBRE OFICIAL
[Signature]
Reedición: No. 100.000.000.000

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

Luz Arriaga de Herber

CONCURRE CON LA FIRMA REGISTRADA POR EL (LOS) EN ESTA NOTARIA

SANTAFE DE BOGOTA, 09 APR 2003



NO SE ASUME RESPONSABILIDAD DEL TEXTO

2003 APR - 09 11:08

JEFE DE NOTARIOS

MINISTERIO DE RELACIONES EXTERIORES

1924542

1924542

CUYA FIRMA APARECE EN EL DOCUMENTO DESEMPERA LAS FUNCIONES INDICADAS

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA CORRESPONDE CON LA ORIGINAL QUE HE TENIDO A LA VISTA

12 FEB 2004

JUAN MANUEL BOTERO MEDINA

NOTARIO

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(19) World Intellectual Property Organization
International Bureau



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31/422, 31/4045, 31/48, A61P 29/00, 25/06 // (A61K
31/517, 31/422) (A61K 31/517, 31/4045) (A61K 31/517,
31/48)

(74) Common Representative: BOEHRINGER INGEL-
HEIM PHARMA KG; Binger Strasse 173, 55216
Ingelheim am Rhein (DE).

(21) International Application Number: PCT/EP02/08993

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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,
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(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
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European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK,
TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (*for all designated States except US*):
BOEHRINGER INGELHEIM PHARMA KG
[DE/DE]; Binger Strasse 173, 55216 Ingelheim am
Rhein (DE).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): DOODS,
Heeri [NL/DE]; Freiherr-von-König-Strasse 6, 88447
Warthausen (DE). RUDOLF, Klaus [DE/DE]; Ochsweg
11, 88447 Warthausen (DE). EBERLEIN, Wolfgang
[DE/DE]; Obere An 6, 88400 Biberach (DE).

Published:
— with international search report

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

(54) Title: USE OF BIBN4096 IN COMBINATION WITH OTHER ANTIMIGRAINE DRUGS FOR THE TREATMENT OF MI-
GRAINE

(57) Abstract: The present invention relates a method of treatment or prevention of headache, migraine or cluster headaches,
which method comprises co-administration of a therapeutically effective amount of the compound A = 1-[N¹-[3,5-Di-
bromo-N-[[4-(3,4-dihydro-2(1 H)-oxochinazolin-3-yl)-1-piperidinyl]-carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine
[BIBN4096BS] or a physiologically acceptable salt thereof and a therapeutically effective amount of a second active antimigraine
drug, particularly sumatriptan, zolmitriptan or dihydroergotamin or a physiologically acceptable salt thereof, as well as to the
corresponding pharmaceutical compositions and the preparation thereof.

WO 03/015787 A1

**Use of BIBN4096 in combination with other antimigraine drugs for the
treatment of migraine**

Field of the invention

Migraine is one of the most common neurological disorders, involving periodical attacks of headache and nausea as well as a plethora of other symptoms. Although considerable progress has been made, the pathophysiology of migraine is still not understood. However, several observations point to an involvement of Calcitonin Gene-Related Peptide (CGRP). Migraine headache involves the activation of the trigeminal system and dilatation of cranial vessels. CGRP is localized to neurons in the trigeminal ganglia and CGRP levels are increased during a migraine attack, presumably causing the vasodilation observed. Accordingly, it is conceivable that inhibition of CGRP-evoked dilatation of the cranial vessels may provide a novel treatment for migraine headache.

Widely used antimigraine drugs are the so-called „triptans“, e.g. sumatriptan and zolmitriptan. These compounds elicit their antimigraine effects due to their vasoconstrictive properties and presumably their inhibition of the release of the neuropeptide calcitonin gene related peptide (CGRP) (Ferrari, M. D., Saxena, P. R. (1995), 5-HT₁ receptors in migraine pathophysiology and treatment, *Eur. J. Neurology*, 2, 5-21; Johnson, K. W., Phebus, L. A., Cohen, M. L. (1998), Serotonin in migraine: Theories, animal models and emerging therapies, *Progress in Drug Research*, Vol. 51, 220-244), the levels of which are assumed to be increased during a migraine attack (Edvinsson, L., Goadsby, P. J. (1994), Neuropeptides in migraine and cluster headache, *Cephalgia*, 14(5), 320-327). A completely novel approach to treat migraine is the use of CGRP antagonists (Doods, H., Hallermeier, G., Wu, D., Entzeroth, M., Rudolf, K., Engel, W., Eberlein, W. (2000), Pharmacological profile of BIBN4096BS, the first selective small molecule CGRP antagonist, *Br. J. Pharmacol.*, 129, 420-423).

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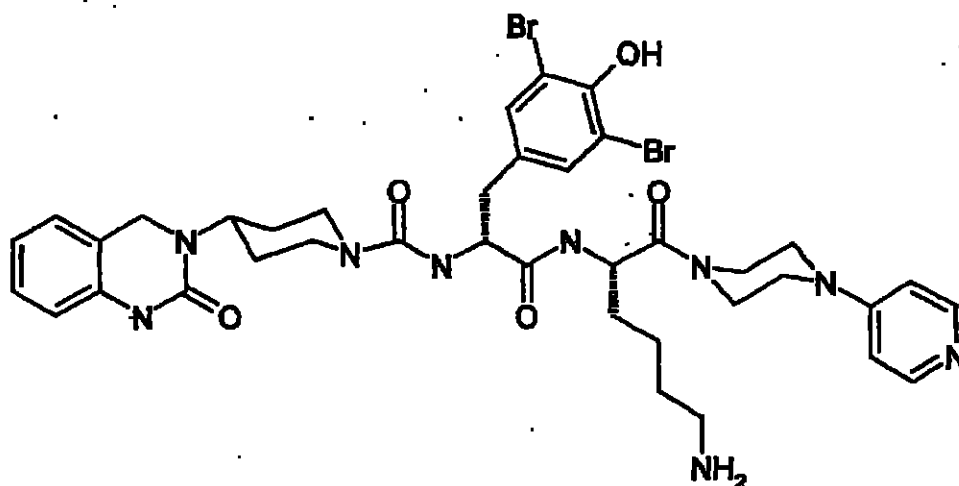
Background of the Invention

WO 98/11128 discloses modified amino acids having CGRP-antagonistic properties, their use and methods for their preparation as well as their use for the production and purification of antibodies and as labelled compounds in RIA and ELISA assays and as diagnostic or analytic auxiliary agents in neurotransmitter research. In view of their pharmacological properties the modified amino acids are thus suitable for acute and prophylactic treatment of headache, particularly migraine and cluster headaches.

Summary of the Invention

Unexpectedly, it was found that in a model which is considered to predict the antimigraine effects of drugs the combination of two drugs with a completely different mode of action, namely a 5-HT_{1B/1D} agonist or an ergot alkaloid and the CGRP antagonist disclosed in the WO 98/11128 A1, namely

A = 1-[N²-[3,5-Dibromo-N-[[4-(3,4-dihydro-2(1H)-oxochinazolin-3-yl)-1-piperidinyl]-carbonyl]-D-tyrosyl]-L-tyryl]-4-(4-pyridinyl)-piperazine [BIBN4096BS],



results in a highly significant better effect compared to the effect of one drug alone.

Detailed Description of the Invention

As a first aspect the present invention provides a method of treatment or prevention of indications selected from the group consisting of headache, migraine and cluster headaches, which method comprises co-administration of a therapeutically effective amount of BIBN4096BS or a physiologically acceptable salt thereof and a therapeutically effective amount of another active antimigraine drug (A) to a person in need of such treatment.

For this purpose, drug (A) can be selected from the group consisting of antiemetics, prokinetics, neuroleptics, antidepressants, neurokinin-antagonists, anti-convulsants, histamine-H₁-receptor antagonists, antimuscarinics, β -blockers, α -agonists and α -antagonists, ergot alkaloids, mild analgesics, non-steroidal antiphlogistics, corticosteroids, calcium-antagonists and 5-HT_{1B/1D}-agonists.

A non-steroidal antiphlogistic may be selected from the group consisting of acclofenac, acemetacin, acetylsalicylic acid, azathioprin, celecoxib, diclofenac, diflunisal, fenbufen, fenoprofen, flurbiprofen, ibuprofen, indometacin, ketoprofen, leflunomide, lornoxicam, mefenamic acid, meloxicam, naproxen, phenylbutazon, piroxicam, sulfasalazin, zomepirac or the pharmaceutically acceptable salts thereof,

as 5-HT_{1B/1D}-agonists may be used, for example, almotriptan, avitriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan or zolmitriptan or the pharmaceutically acceptable salts thereof and

suitable ergot alkaloids are, for example, ergotamine and dihydroergotamine.

Additional active substances which may be considered for the above-mentioned combinations as drug (A) component include, for example, metoclopramide, domperidon, diphenhydramine, cyclizine, promethazine, chlorpromazine, dexamethasone, flunarizine, dextropropoxyphene, meperidine, propranolol, nadolol, atenolol, clonidine, indoramine, carbamazepine, phenytoin, valproate, amitriptylin, lidocaine or diltiazem.

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As a preferred embodiment in the method according to the invention drug (A) is selected from the group consisting of ergot alkaloids and 5-HT_{1B/1D}-agonists, especially preferred are dihydroergotamine, sumatriptan and zolmitriptan, most preferred is sumatriptan or the physiologically acceptable salts thereof.

5

As a further preferred embodiment in the method according to the invention drug (A) is selected from the group consisting of non-steroidal antiphlogistics, especially preferred is meloxicam or the physiologically acceptable salts thereof.

- 10 The dosage for the combined migraine drug (A) is appropriately 1/50 of the lowest dose normally recommended up to 1/1 of the normally recommended dosage, preferably 1/50 to 1/6 and more preferably 1/20 to 1/10, by orally, nasally, subcutaneous or intravenous route. The normally recommended dose for the combined migraine drug (A) should be understood to be the dose disclosed in Rote
- 15 Liste Win® 2001/1, Editio Cantor Verlag Aulendorf.

According to the invention BIBN4096BS or a physiologically acceptable salt thereof may be administered by intravenous or subcutaneous route in a dosage of 0.0001 to 3 mg/kg of body weight or by oral, nasal or inhalative route in a dosage of 0.1 to 10

20 mg/kg of body weight once, twice or trice a day, in combination with

sumatriptan or a physiologically acceptable salt thereof which may be administered by oral route in a dosage of 0.03 to 1.43 mg/kg of body weight once, twice or trice a day or

25

by intravenous or subcutaneous route in a dosage of 0.002 to 0.09 mg/kg of body weight once or twice a day or

30

by rectal route in a dosage of 0.007 to 0.36 mg/kg of body weight once or twice a day or

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by nasal route in a dosage of 0.006 to 0.29 mg/kg of body weight once or twice a day or in combination with

5 Zolmitriptan or a physiologically acceptable salt thereof which may be administered by oral route in a dosage of 0.0007 to 0.036 mg/kg of body weight once or twice a day or

10 in combination with dihydroergotamine or a physiologically acceptable salt thereof which may be administered by oral route in a dosage of 0.001 to 0.07 mg/kg of body weight once or twice a day or

15 in combination with meloxicam or a physiologically acceptable salt thereof which may be administered by oral route in a dosage of 0.004 to 0.21 mg/kg of body weight once a day.

20 In a preferred embodiment of the invention BIBN4096BS or a physiologically acceptable salt thereof may be administered by intravenous or subcutaneous route in a dosage of 0.0001 to 3 mg/kg of body weight or by oral, nasal or inhalative route in a dosage of 0.1 to 10 mg/kg of body weight once, twice or trice a day, in combination with

25 sumatriptan or a physiologically acceptable salt thereof which may be administered by oral route in a dosage of 0.03 to 0.24 mg/kg of body weight once, twice or trice a day or

by intravenous or subcutaneous route in a dosage of 0.002 to 0.015 mg/kg of body weight once or twice a day or

30 by rectal route in a dosage of 0.007 to 0.06 mg/kg of body weight once or twice a day or

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by nasal route in a dosage of 0.006 to 0.048 mg/kg of body weight once or twice a day or

5 In combination with Zolmitriptan or a physiologically acceptable salt thereof which may be administered by oral route in a dosage of 0.0007 to 0.006 mg/kg of body weight once or twice a day or

10 In combination with dihydroergotamine or a physiologically acceptable salt thereof which may be administered by oral route in a dosage of 0.001 to 0.01 mg/kg of body weight once or twice a day or

15 in combination with meloxicam or a physiologically acceptable salt thereof which may be administered by oral route in a dosage of 0.004 to 0.036 mg/kg of body weight once a day.

20 In a more preferred embodiment of the invention BIBN4096BS or a physiologically acceptable salt thereof may be administered by intravenous or subcutaneous route in a dosage of 0.0001 to 3 mg/kg of body weight or by oral, nasal or inhalative route in a dosage of 0.1 to 10 mg/kg of body weight once, twice or trice a day, in combination with

25 sumatriptan or a physiologically acceptable salt thereof which may be administered by oral route in a dosage of 0.075 to 0.143 mg/kg of body weight once, twice or trice a day or

by intravenous or subcutaneous route in a dosage of 0.005 to 0.009 mg/kg of body weight once or twice a day or

30 by rectal route in a dosage of 0.0175 to 0.036 mg/kg of body weight once or twice a day or

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by nasal route in a dosage of 0.015 to 0.029 mg/kg of body weight once or twice a day or

5 in combination with Zolmitriptan or a physiologically acceptable salt thereof which may be administered by oral route in a dosage of 0.00175 to 0.0036 mg/kg of body weight once or twice a day or

10 in combination with dihydroergotamine or a physiologically acceptable salt thereof which may be administered by oral route in a dosage of 0.0025 to 0.007 mg/kg of body weight once or twice a day or

15 in combination with meloxicam or a physiologically acceptable salt thereof which may be administered by oral route in a dosage of 0.01 to 0.02 mg/kg of body weight once a day.

The present invention provides as a second aspect a pharmaceutical composition for treating or preventing headache, migraine or cluster headaches comprising a therapeutically effective amount of BIBN4096BS or a physiologically acceptable salt thereof and an antimigraine drug (A) selected from the group consisting of
20 sumatriptan, zolmitriptan and dihydroergotamin or a physiologically acceptable salt thereof as a combined preparation for simultaneous or sequential administration.

A pharmaceutical composition according to the invention may comprise a single dosage unit of 0.1 to 10 mg of BIBN4096BS and

25 a single dosage unit of 1 to 100 mg of sumatriptan or

a single dosage unit of 0.1 to 2.5 mg of zolmitriptan or

30 a single dosage unit of 0.1 to 5 mg of dihydroergotamin or

a single dosage unit of 7.5 to 15 mg of meloxicam.

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All doses or dosage units of a physiologically acceptable salt of an active compound mentioned hereinbefore should be understood as the dose or dosage of the active compound itself.

5

Furthermore, a pharmaceutical composition according to the invention may be a kit of parts for treating or preventing headache, migraine or cluster headaches, which kit comprises

- 10 (a) a first containment containing a pharmaceutical composition comprising a therapeutically effective amount of BIBN4096BS or a physiologically acceptable salt thereof and one or more pharmaceutically acceptable diluents and/or carriers; and
- (b) a second containment containing a pharmaceutical composition comprising sumatriptan, zolmitriptan or dihydroergotamin or a
15 physiologically acceptable salt thereof and one or more pharmaceutically acceptable diluents and/or carriers.

A preferred kit of parts comprises sumatriptan in the second containment.

- 20 A third aspect of the present invention is the use of BIBN4096BS or a physiologically acceptable salt thereof in combination with another active antimigraine drug (A) for the manufacture of a pharmaceutical composition for treating or preventing headache, migraine or cluster headaches. Drug (A) and preferred embodiments thereof as well as pharmaceutical compositions are
25 mentioned hereinbefore under the first and second aspect of the invention. Most preferred with respect to all aspects of the invention is the combination of BIBN4096BS with sumatriptan or of physiologically acceptable salts thereof.

- Several of the drug (A) components mentioned hereinbefore are already on the
30 market, e.g. sumatriptan is sold under the trade name imigran®, zolmitriptan is sold under the trade name ascotop® and dihydroergotamin and the pharmaceutically acceptable salts thereof under the trade name agit®.

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BIBN4096BS can be administered using for instance pharmaceutical formulations disclosed in WO 98/11128 or using one of the following pharmaceutical formulations:

- 5 capsules for powder inhalation containing 1 mg of active substance,
- inhalable solution for nebulisers containing 1 mg of active substance,
- propellant gas-operated metering aerosol containing 1 mg of active substance,
- 10 nasal spray containing 1 mg of active substance,
- tablets containing 20 mg of active substance,
- 15 capsules containing 20 mg of active substance,
- aqueous solution for nasal application containing 10 mg of active substance,
- aqueous solution for nasal application containing 5 mg of active substance, or
- 20 suspension for nasal application containing 20 mg of active substance.

Example 1

- 25 In order to examine the pharmacological activity of combinations according to the invention the following experiments have been carried out

Measurement of facial skin blood flow

- 30 Facial skin blood flow was measured by a modified method described by Escott et al. (Escott, K. J., Beattie, D. T., Connor, H. E., Brain, S. D. (1995), Trigeminal ganglion stimulation increases facial skin blood flow in the rat: a major role for calcitonin gene-related peptide, *Brain Research*, 669(1), 93-99). Fasted male wistar

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rats (strain CHbb:THOM, 280-320g) were anaesthetized with sodium pentobarbitone (initially with 60 mg/kg i.p. and maintained throughout the experiment with an intraperitoneal infusion of 30 mg/kg/h through a 23 G needle using a solution of 10 mg/ml). Both sides of the buccal area of the facial skin were shaved and depilated with a commercial depilatory cream (Pilca, Schwarzkopf & Henkel, 40551 Düsseldorf, Germany). The trachea was cannulated and the animals were artificially respired (80 strokes/min) with room air supplemented with oxygen. The body temperature was maintained at 37°C by an automated heating pad. The left femoral artery and the left femoral vein were cannulated for the continuous measurement of arterial blood pressure and intravenous administration of test compounds, respectively. Neuromuscular blockade was achieved by intravenous administration of pancuronium bromide (1mg/kg/0.5ml, 5 min prior to each electrical stimulation). Heart rate was derived from the blood pressure signal. Blood pressure and heart rate were continuously monitored throughout the course of the experiment to assess the level of anaesthesia and to monitor the cardiovascular effects of the drugs used in this study.

The animals were placed in a stereotaxic frame and a longitudinal incision was made in the scalp. A small hole was drilled in the skull (left or right) and a bipolar electrode (Rhodes SNEX-100 supplied by David Kopf Instruments, Tujunga, 91042 California, U.S.A.) was lowered using a micromanipulator, into the trigeminal ganglion (0.32 cm dorsal to bregma, $\pm$ 0.30 cm lateral from the midline and 0.95 cm below the dural surface). The position of the electrodes in the trigeminal ganglia were checked visually at the end of each experiment following removal of the brain. The trigeminal ganglion was stimulated at 10 Hz, 1 mA, 1 msec for 30 seconds using a stimulator supplied by Hugo Sachs Elektronik (79232 March-Hugstetten, Germany). Microvascular blood flow changes in the facial skin were measured by Laser Doppler flowmetry with a Periflux laser doppler system (PeriFLUX 4001, wave length 780 nm; time constant 3 s, Perimed AB, Järfälla, S-17526, Sweden). Standard laser doppler probes (PROBE 408) were positioned on either side of the face approximately 0.5 cm below the centre of the eye, an area innervated by the maxillary branch (V2) of the trigeminal nerve. Blood flow changes were measured

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as flux in arbitrary units and expressed as area under the flux curve (mm²) according to Escott et al. (1995).

Experimental protocol

- 5 After 30 min of equilibration, the animals were subjected to three periods of electrical stimulation, separated by a 30 min interval. The first stimulation was used as a control for the subsequent stimulations. Saline, single compound or the combination were administered intravenously 5 min prior to the second stimulation.
- 10 The results are given in the following table 1. They show that the improved potency of the combination of 5-HT_{1B/1D} agonists or other antimigraine drugs in general with a CGRP antagonist would allow higher efficacy, would allow lower doses of each compound resulting in similar efficacy with less side effects and the addition of the two mechanisms might result in less headache recurrence.

15

Table 1: Effect of BIBN 4096 BS in combination with other antimigraine drugs on facial skin vasodilation induced by electrical trigeminal ganglion stimulation in the rat

treatment	% of trigeminal stimulation	n	% inhibition compared to control value
saline (control)	82.7 ± 4.4	11	-
BIBN 4096 BS (0.03 mg/kg)	60.3 ± 5.1	8	27.1
Sumatriptan (1.0 mg/kg)	68.8 ± 6.8	7	16.8
BIBN 4096 BS + Sumatriptan (0.03 mg + 1.0 mg)/kg	28.6 ± 5.4 ^a	6	67.8
Zolmitriptan (0.1 mg/kg)	55.6 ± 4.8	6	32.8
BIBN 4096 BS + Zolmitriptan (0.03 mg + 0.1 mg)/kg	27.3 ± 6.0 ^b	6	67.0
DHE (0.1 mg/kg)	60.4 ± 4.1	6	27.0
BIBN 4096 BS + DHE (0.03 mg + 0.1 mg)/kg	20.9 ± 3.1 ^c	6	74.7

DHE = Dihydroergotamin

^a significant, p < 0.001, compared to Sumatriptan

^b significant, p < 0.01, compared to Zolmitriptan

^c significant, p < 0.001, compared to DHE

The Examples which follow describe pharmaceutical preparations which contain as active substance BIBN4096BS or a pharmaceutically acceptable salt thereof:

5 Example 2

Capsules for powder inhalation with 1 mg of active substance

Composition:

10 1 capsule for powder inhalation contains:

active substance	1.0 mg
lactose	20.0 mg
hard gelatine capsules	<u>50.0 mg</u>
	71.0 mg

15

Method of preparation:

The active substance is ground to the particle size needed for inhalation. The ground active substance is homogeneously mixed with the lactose. The mixture is packed into hard gelatine capsules.

20

Example 3

Inhalable solution for Respimat® with 1 mg of active substance

25 Composition:

1 spray contains:

active substance	1.0 mg
benzalkonium chloride	0.002 mg
disodium edetate	0.0075 mg
30 purified water ad	15.0 µl

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Method of preparation:

The active substance and benzalkonium chloride are dissolved in water and packed in Resplimat® cartridges.

5 Example 4

Inhalable solution for nebulisers with 1 mg of active substance

Composition:

10 1 vial contains:

active substance	0.1 g
sodium chloride	0.18 g
benzalkonium chloride	0.002 g
purified water ad	20.0 ml

15

Method of preparation:

Active substance, sodium chloride and benzalkonium chloride are dissolved in water.

20 Example 5

Propellant gas-operated metering aerosol with 1 mg of active substance

Composition:

25 1 spray contains:

active substance	1.0 mg
lecithin	0.1 %
propellant gas ad	50.0 µl

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Method of preparation:

The micronised active substance is homogeneously suspended in the mixture of lecithin and propellant gas. The suspension is transferred into a pressurised container with a metering valve.

5

Example 6

Nasal spray with 1 mg of active substance

10 Composition:

1 spray jet contains

active substance	1.0 mg
mannitol	5.0 mg
disodium edetate	0.05 mg
15 ascorbic acid	1.0 mg
purified water ad	0.1 ml

Method of preparation:

The active substance and the excipients are dissolved in water and transferred into
20 a suitable container.

Example 7

Injectable solution with 5 mg of active substance per 5 ml

25

Composition:

active substance in basic form	5 mg
acid/salt-forming agent in the amount needed to form a neutral salt	q.s.
30 glucose	250 mg
human serum albumin	10 mg
glycofurol	250 mg

water for injections ad

5 ml

Preparation:

Dissolve the glycofurol and glucose in water for injections (Wfi); add human serum
5 albumin; add salt-forming agent; dissolve active substance with heating; make up to
specified volume with Wfi; transfer into ampoules under nitrogen gas.

Example 8

10 Injectable solution for subcutaneous administration containing 5 mg of active
substance per 1 ml

Composition:

active substance	5 mg
15 glucose	50 mg
polysorbate 80 = Tween 80	2 mg
water for injections ad	1 ml

Preparation:

20 Dissolve glucose and polysorbate in water for injections; dissolve active substance
with heating or using ultrasound; make up to specified volume with Wfi; transfer into
ampoules under inert gas.

Example 9

25

Injectable solution containing 100 mg of active substance per 10 ml

Composition:

active substance	100 mg
30 monopotassium dihydrogen phosphate = KH_2PO_4	12 mg
disodium hydrogen phosphate	

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	= Na ₂ HPO ₄ ·2H ₂ O	2 mg
	sodium chloride	180 mg
	human serum albumin	50 mg
	polysorbate 80	20 mg
5	water for injections ad	10 ml

Preparation:

Dissolve polysorbate 80, sodium chloride, monopotassium dihydrogen phosphate and disodium hydrogen phosphate in water for injections (Wfi); add human serum
10 albumin; dissolve active substance with heating; make up to specified volume with Wfi; transfer into ampoules.

Example 10

15 Lyophilisate containing 10 mg of active substance

Composition:

	active substance in basic form	10 mg
	acid/salt-forming agent in the amount needed	
20	to form a neutral salt	q.s.
	mannitol	300 mg
	water for injections ad	2 ml

Preparation:

25 Dissolve mannitol in water for injections (Wfi); add salt-forming agent; dissolve active substance with heating; make up to specified volume with Wfi; transfer into vials; freeze-dry.

Solvent for lyophilisate:

30	polysorbate 80 = Tween 80	20 mg
	mannitol	200 mg
	water for injections ad	10 ml

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Preparation:

Dissolve polysorbate 80 and mannitol in water for injections (Wfi); transfer into ampoules.

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Example 11

Lyophilisate containing 5 mg of active substance

10 Composition:

active substance in basic form	5 mg
polar or nonpolar solvent (which can be removed by freeze-drying) ad	1 ml

15

Preparation:

Dissolve active substance in suitable solvent; transfer into vials; freeze-dry.

Solvent for lyophilisate:

20 polysorbate 80 = Tween 80	5 mg
mannitol	100 mg
water for injections ad	2 ml

Preparation:

25 Dissolve polysorbate 80 and mannitol in water for injections (Wfi); transfer into ampoules.

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Example 12

Tablets containing 20 mg of active substance

5	Composition:	
	active substance	20 mg
	lactose	120 mg
	maize starch	40 mg
	magnesium stearate	2 mg
10	Povidone K 25	18 mg

Preparation:

Homogeneously mix the active substance, lactose and maize starch; granulate with an aqueous solution of Povidone; mix with magnesium stearate; press in a tablet press; weight of tablet 200 mg.

Example 13

Capsules containing 20 mg of active substance

20	Composition:	
	active substance	20 mg
	maize starch	80 mg
	highly dispersed silica	5 mg
25	magnesium stearate	2.5 mg

Preparation:

Homogeneously mix the active substance, maize starch and silica; mix with magnesium stearate; transfer mixture into size 3 hard gelatine capsules in a capsule filling machine.

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Example 14

Suppositories containing 50 mg of active substance

5 **Composition:**

active substance	50 mg
hard fat (Adeps solidus) q.s. ad	1700 mg

Preparation:

- 10 Melt the hard fat at about 38°C; homogeneously disperse the ground active substance in the molten hard fat; after cooling to about 35°C, pour into chilled moulds.

Example 15

15 Aqueous solution for nasal administration containing 10 mg of active substance

Composition:

active substance	10.0 mg
hydrochloric acid in the amount needed to form a neutral salt	
20 methyl parahydroxybenzoate (PHB)	0.01 mg
propyl parahydroxybenzoate (PHB)	0.005 mg
purified water ad	1.0 ml

Preparation:

- 25 The active substance is dissolved in purified water; hydrochloric acid is added until the solution is clear; methyl and propyl PHB are added; the solution is made up to the specified volume with purified water; the solution is filtered sterile and transferred into a suitable container.

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Example 16

Aqueous solution for nasal administration containing 5 mg of active substance

5	Composition:	
	active substance	5 mg
	1,2-propanediol	300 mg
	hydroxyethylcellulose	5 mg
	sorbic acid	1 mg
10	purified water ad	1 ml

Preparation:

The active substance is dissolved in 1,2-propanediol; a hydroxyethyl-cellulose solution in purified water containing sorbic acid is prepared and added to the solution of active substance; the solution is filtered sterile and transferred into a suitable container.

Example 17

20 Aqueous solution for intravenous administration containing 5 mg of active substance

	Composition:	
	active substance	5 mg
	1,2-propanediol	300 mg
25	mannitol	50 mg
	water for injections (Wfi) ad	1 ml

Preparation:

The active substance is dissolved in 1,2-propanediol; the solution is made up to approximately the specified volume with Wfi; the mannitol is added and made up to approximately the specified volume with Wfi; the solution is filtered sterile, transferred into individual containers and autoclaved.

Example 18

Liposomal formulation for intravenous injection containing 7.5 mg of active substance

5

Composition:

	active substance	7.5 mg
	egg lecithin, e.g. Lipoid E 80	100.0 mg
	cholesterol	50.0 mg
10	glycerol	50.0 mg
	water for injections ad	1.0 ml

Preparation:

The active substance is dissolved in a mixture of lecithin and cholesterol; the
15 solution is added to a mixture of glycerol and WFI and homogenised by high
pressure homogenisation or by the Microfluidizer technique; the liposomal
formulation obtained is transferred into a suitable container under aseptic
conditions.

20 **Example 19**

Suspension for nasal administration containing 20 mg of active substance

Composition:

25	active substance	20.0 mg
	carboxymethylcellulose (CMC)	20.0 mg
	sodium monohydrogen phosphate/sodium	
	dihydrogen phosphate buffer pH 6.8.	q.s....
	sodium chloride	8.0 mg
30	methyl parahydroxybenzoate	0.01 mg
	propyl parahydroxybenzoate	0.003 mg
	purified water ad	1.0 ml

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30

Preparation:

The active substance is suspended in an aqueous CMC solution; the other ingredients are added successively to the suspension and the suspension is topped up
5 to the specified volume with purified water.

Example 20

Aqueous solution for subcutaneous administration with 10 mg of active substance

10

Composition:

active substance	10.0 mg
sodium monohydrogen phosphate/sodium	
dihydrogen phosphate buffer q.s. ad pH	7.0
15 sodium chloride	4.0 mg
water for injections ad	0.5 ml

Preparation:

The active substance is dissolved in the phosphate buffer solution, after the addition
20 of the common salt the solution is made up to the specified volume with water. The solution is filtered sterile, transferred into a suitable container and autoclaved.

Example 21

25 **Aqueous suspension for subcutaneous administration containing 5 mg of active substance**

Composition:

active substance	5.0 mg
30 polysorbate 80	0.5 mg
water for injections	0.5 ml

Preparation:

The active substance is suspended in the polysorbate 80 solution and comminuted to a particle size of about 1 μm using a suitable dispersing technique (e.g. wet grinding, high pressure homogenisation, microfluidisation, etc.). The suspension is transferred into a corresponding container under aseptic conditions.

Patent Claims

1. A method of treatment or prevention of indications selected from the group
5 consisting of headache, migraine and cluster headaches, which method comprises
co-administration of a therapeutically effective amount of BIBN4096BS or a
physiologically acceptable salt thereof and a therapeutically effective amount of
another active antimigraine drug (A) to a person in need of such treatment.
- 10 2. The method according to claim 1, characterized in that drug (A) is selected from
the group consisting of antiemetics, prokinetics, neuroleptics, antidepressants,
neurokinin-antagonists, anti-convulsants, histamine-H₁-receptor antagonists,
antimuscarinics, β -blockers, α -agonists and α -antagonists, ergot alkaloids, mild
analgesics, non-steroidal antiphlogistics, corticosteroids, calcium-antagonists and
15 5-HT_{1B/1D}-agonists.
3. The method according to claim 2, characterized in that drug (A) is selected from
the group consisting of ergot alkaloids and 5-HT_{1B/1D}-agonists.
- 20 4. The method according to claim 3, characterized in that the ergot alkaloid is
ergotamine or dihydroergotamine or a physiologically acceptable salt thereof and
the 5-HT_{1B/1D}-agonist is almotriptan, avitriptan, eletriptan, frovatriptan, naratriptan,
rizatriptan, sumatriptan or zolmitriptan or a physiologically acceptable salt thereof.
- 25 5. The method according to claim 1, characterized in that drug (A) is sumatriptan,
zolmitriptan or dihydroergotamine or a physiologically acceptable salt thereof.
6. The method of claim 5, characterized in that BIBN4096BS or a physiologically
acceptable salt thereof is administered by intravenous or subcutaneous route in a
30 dosage of 0.0001 to 3 mg/kg of body weight or by oral, nasal or inhalative route in a
dosage of 0.1 to 10 mg/kg of body weight once, twice or trice a day and

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sumatriptan or a physiologically acceptable salt thereof is administered by oral route in a dosage of 0.03 to 1.43 mg/kg of body weight once, twice or trice a day or

5 by intravenous or subcutaneous route in a dosage of 0.002 to 0.09 mg/kg of body weight once or twice a day or

by rectal route in a dosage of 0.007 to 0.36 mg/kg of body weight once or twice a day or

10 by nasal route in a dosage of 0.006 to 0.29 mg/kg of body weight once or twice a day or

Zolmitriptan or a physiologically acceptable salt thereof is administered by oral route in a dosage of 0.0007 to 0.036 mg/kg of body weight once or twice a day or

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dihydroergotamine or a physiologically acceptable salt thereof is administered by oral route in a dosage of 0.001 to 0.07 mg/kg of body weight once or twice a day.

7. A pharmaceutical composition for treating or preventing headache, migraine or cluster headaches comprising a therapeutically effective amount of BIBN4096BS or 20 a physiologically acceptable salt thereof and an antimigraine drug (A) selected from the group consisting of sumatriptan, zolmitriptan and dihydroergotamin or a physiologically acceptable salt thereof as a combined preparation for simultaneous or sequential administration.

25

8. The pharmaceutical composition of claim 7 comprising a single dosage unit of 0.1 to 10 mg of BIBN4096BS and

a single dosage unit of 1 to 100 mg of sumatriptan or

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a single dosage unit of 0.1 to 2.5 mg of zolmitriptan or

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a single dosage unit of 0.1 to 5 mg of dihydroergotamin.

9. A kit of parts for treating or preventing headache, migraine or cluster headaches; which kit comprises

- 5 (c) a first containment containing a pharmaceutical composition comprising a therapeutically effective amount of BIBN4096BS or a physiologically acceptable salt thereof and one or more pharmaceutically acceptable diluents and/or carriers; and
- (d) a second containment containing a pharmaceutical composition
10 comprising sumatriptan, zolmitriptan or dihydroergotamin or a physiologically acceptable salt thereof and one or more pharmaceutically acceptable diluents and/or carriers.

10. The kit of parts according to claim 9, which kit comprises sumatriptan or a
15 physiologically acceptable salt thereof in the second containment.

11. Use of BIBN4096BS or a physiologically acceptable salt thereof in combination with another active antimigraine drug (A) for the manufacture of a pharmaceutical composition for treating or preventing headache, migraine or cluster headaches.

20 12. The use according to claim 11, characterized in that drug (A) is selected from the group consisting of antiemetics, prokinetics, neuroleptics, antidepressants, neurokinin-antagonists, anti-convulsants, histamine-H1-receptor antagonists, antimuscarinics, β -blockers, α -agonists and α -antagonists, ergot alkaloids, mild
25 analgesics, non-steroidal antiphlogistics, corticosteroids, calcium-antagonists and 5-HT_{1B/1D}-agonists.

13. The use according to claim 12, characterized in that drug (A) is selected from the group consisting of 5-HT_{1B/1D}-agonists and ergot alkaloids.

30 14. The use according to claim 13, characterized in that the ergot alkaloid is ergotamine or dihydroergotamine or a physiologically acceptable salt thereof and

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the of 5-HT_{1B/1D}-agonist is almotriptan, avitriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan or zolmitriptan or a physiologically acceptable salt thereof.

15. The use according to claim 14, characterized in that drug (A) is sumatriptan,
5 zolmitriptan or dihydroergotamin or a physiologically acceptable salt thereof.

16. The use of BIBN4096BS or a physiologically acceptable salt thereof for
manufacture of a pharmaceutical composition or a kit of parts according to any of
claims 7 to 10.

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INTERNATIONAL SEARCH REPORT

Info 1 Application No
PCT/EP 02/08993

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/517 A61K31/422 A61K31/4045 A61K31/48 A61P29/00
A61P25/06 //(A61K31/517,31:422),(A61K31/517,31:4045),
(A61K31/517,31:48)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61P A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DOODS H ET AL: "PHARMACOLOGICAL PROFILE OF BIBN4096BS, THE FIRST SELECTIVE SMALL MOLECULE CGRP ANTAGONIST" BRITISH JOURNAL OF PHARMACOLOGY, BASINGSTOKE, HANTS, GB, vol. 129, no. 3, 2000, pages 420-423, XP000992559 ISSN: 0007-1188 abstract	1-4, 11-13,16
A		5-10,14, 15

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to underlain the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, each combination being obvious to a person skilled in the art

"Z" document member of the same patent family

Date of the actual completion of the international search

18 November 2002

Date of mailing of the international search report

27/11/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patenplein 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 apo nl,
Fax. (+31-70) 340-0016

Authorized officer

Herrera, S

INTERNATIONAL SEARCH REPORT

Inter of Application No
PCT/EP 02/08993

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	FERRARI M D ET AL: "Oral triptans (serotonin 5-HT _{1B/1D} agonists) in acute migraine treatment: a meta-analysis of 53 trials" LANCET, XX, XX, vol. 358, no. 9294, 17 November 2001 (2001-11-17), pages 1668-1675, XP004323637 ISSN: 0140-6736	1-4, 11-13,16
A	abstract	5-10,14, 15
Y	DATABASE MEDLINE 'Online! 15 November 1993 (1993-11-15) HOERNECKE R ET AL: "'Treatment of migraine attacks: combination of dihydroergotamine tartrate and paracetamol in comparison with individual drugs and placebo" Database accession no. NLM8295604 XP002199881	1-4, 11-13,16
A	abstract	5-10,14, 15
Y	& MEDIZINISCHE KLINIK (MUNICH, GERMANY: 1983) GERMANY 15 NOV 1993, vol. 88, no. 11, 15 November 1993 (1993-11-15), pages 642-648, ISSN: 0723-5003	
Y	DATABASE MEDLINE 'Online! January 1992 (1992-01) SAADAH H A: "Abortive headache therapy with intramuscular dihydroergotamine." Database accession no. NLM1555927 XP002216638	1-4, 11-13,16
A	abstract	5-10,14, 15
A	& HEADACHE. UNITED STATES JAN 1992, vol. 32, no. 1, January 1992 (1992-01), pages 18-20, ISSN: 0017-8748	
A	WO 01 10425 A (BOEHRINGER INGELHEIM PHARMA ;EBERLEIN WOLFGANG (DE); DOODS HENRI () 15 February 2001 (2001-02-15) claims	1-16
A	WO 98 11128 A (EBERLEIN WOLFGANG ;ENTZERTH MICHAEL (DE); HALLERMAYER GERHARD (DE) 19 March 1998 (1998-03-19) cited in the application page 173, line 6-11	1-16

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/08993

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependant claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

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International Application No. PCT/EP 02 08993

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 1-6 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 02/08993

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0110425 A	15-02-2001	DE 19937304 A1	15-03-2001
		AU 6992800 A	05-03-2001
		BE 6391 A	30-09-2002
		BR 0013009 A	30-04-2002
		CN 1370069 T	18-09-2002
		CZ 20020497 A3	12-06-2002
		WO 0110425 A2	15-02-2001
		EP 1207884 A2	29-05-2002
		NO 20020605 A	07-02-2002
		SK 1972002 A3	04-06-2002
		TR 200200359 T2	21-05-2002
WO 9811128 A	19-03-1998	DE 19636623 A1	12-03-1998
		DE 19720011 A1	19-11-1998
		AU 721035 B2	22-06-2000
		AU 4119697 A	02-04-1998
		BE 103250 A	31-05-2000
		BR 9712023 A	31-08-1999
		CN 1230196 A	29-09-1999
		CZ 9900823 A3	16-06-1999
		EE 9900115 A	15-10-1999
		WO 9811128 A1	19-03-1998
		EP 0927192 A1	07-07-1999
		HR 970481 A1	31-08-1998
		JP 2000505100 T	25-04-2000
		NO 991130 A	05-05-1999
		NZ 334543 A	23-06-2000
		PL 331989 A1	16-08-1999
		SK 29799 A3	13-03-2000
		TR 9900537 T2	21-07-1999
		US 6344449 B1	05-02-2002
		ZA 9708083 A	17-12-1999
		HU 9904501 A2	28-04-2000

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

IPEA/ _____

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:

The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only	
Identification of IPEA	Date of receipt of DEMAND
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION	
Applicant's or agent's file reference 1/1248	
International application No. PCT/EP 02/088983	International filing date (day/month/year) 10/08/2002
(Earliest) Priority date (day/month/year) 17/08/2001	
Title of invention Use of BIBN4096 in combination with other antimigraine drugs for the treatment of migraine	
Box No. II APPLICANT(S)	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)	
Boehringer Ingelheim Pharma KG	
D-55216 Ingelheim/Rhein	
Telephone No. 07351-54-4408	
Facsimile No. 07351-54-4377	
Teleprinter No.	
Applicant's registration No. with the Office	
State (that is, country) of nationality: DE	State (that is, country) of residence: DE
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)	
DOODS Henri Freiherr-von-König-Straße 6 88447 Warthausen	
State (that is, country) of nationality: NL	State (that is, country) of residence: DE
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)	
RUDOLF Klaus Oechweg 11 88447 Warthausen	
State (that is, country) of nationality: DE	State (that is, country) of residence: DE
☒ Further applicants are indicated on a continuation sheet.	

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Sheet No. 2.

International application No.
PCT/EP 02/08993

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

EBERLEIN Wolfgang
Obere Au 6
88400 Biberach

State *(that is, country)* of nationality:
DE

State *(that is, country)* of residence:
DE

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

☐ Further applicants are indicated on another continuation sheet.

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☐ agent ☐ common representativeand ☐ has been appointed earlier and represents the applicant(s) also for international preliminary examination.☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.Name and address: (Family name followed by given name; for a legal entity, full official designation.
The address must include postal code and name of country.)

BOEHRINGER INGELHEIM GMBH

D-55216 Ingelheim/Rhein

Telephone No.

07351-54-4408

Facsimile No.

07351-54-4377

Teleprinter No.

Agent's registration No. with the Office

☒ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

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

☒ the international application as originally filedthe description ☒ as originally filed☐ as amended under Article 34the claims ☒ as originally filed☐ as amended under Article 19 (together with any accompanying statement)☐ as amended under Article 34the drawings ☐ as originally filed☐ as amended under Article 342. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). (This check-box may be marked only where the time limit under Article 19 has not yet expired.)

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

Language for the purposes of international preliminary examination: English

☒ which is the language in which the international application was filed.☐ which is the language of a translation furnished for the purposes of international search.☐ which is the language of publication of the international application.☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The applicant hereby elects all eligible States (that is, all States which have been designated and which are bound by Chapter II of the PCT)

excluding the following States which the applicant wishes not to elect:

Sheet No. 4.

International application No.
PCT/EP 02/08993

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

- | | | |
|--|---|----------|
| 1. translation of international application | : | sheets |
| 2. amendments under Article 34 | : | sheets |
| 3. copy (or, where required, translation) of amendments under Article 19 | : | sheets |
| 4. copy (or, where required, translation) of statement under Article 19 | : | sheets |
| 5. letter | : | 1 sheets |
| 6. other (specify) | : | sheets |

For International Preliminary Examining Authority use only

received not received

- | | |
|--------------------------|--------------------------|
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |

The demand is also accompanied by the item(s) marked below:

- | | |
|--|---|
| 1. ☒ fee calculation sheet | 5. ☐ statement explaining lack of signature |
| 2. ☐ original separate power of attorney | 6. ☐ sequence listings in computer readable form |
| 3. ☐ original general power of attorney | 7. ☐ tables in computer readable form related to sequence listings |
| 4. ☐ copy of general power of attorney; reference number, if any: | 8. ☐ other (specify): |

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).



ROTHERMEL Reinfried
European Patent Attorney
GA 38990

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. ☐ The applicant has been informed accordingly.

4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.

5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

PCT

REQUEST

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

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) 1/1248

Box No. I TITLE OF INVENTION

Use of BIBN4098 in combination with other antimigraine drugs for the treatment of migraine

Box No. II APPLICANT

☐ This person is also inventor

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence (if no State of residence is indicated below.)

BOEHRINGER INGELHEIM PHARMA KG
Binger Straße 173

55216 Ingelheim am Rhein
DE

Telephone No.
07351-54-4408

Facsimile No.
07351-54-4377

Teleprinter No.

Applicant's registration No. with the Office

State (that is, country) of nationality:
DE

State (that is, country) of residence:
DE

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence (if no State of residence is indicated below.)

DOODS, Henri
Freiherr-von-König-Straße 6
D-88447 Warthausen
DE

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only (if this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:
NL

State (that is, country) of residence:
DE

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:

☐ agent

☒ common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

BOEHRINGER INGELHEIM PHARMA KG
Binger Straße 173

55216 Ingelheim am Rhein
DE

Telephone No.
07351-54-4408

Facsimile No.
07351-54-4377

Teleprinter No.

Agent's registration No. with the Office

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Sheet No. ...2...

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)	
<i>If none of the following sub-boxes is used, this sheet should not be included in the request.</i>	
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i> RUDOLF, Klaus Öschweg 11 D-88447 Warthausen DE	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State <i>(that is, country)</i> of nationality: DE	State <i>(that is, country)</i> of residence: DE
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i> EBERLEIN, Wolfgang Obere Au 6 D-88400 Biberach DE	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State <i>(that is, country)</i> of nationality: DE	State <i>(that is, country)</i> of residence: DE
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i> 	This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State <i>(that is, country)</i> of nationality:	State <i>(that is, country)</i> of residence:
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i> 	This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State <i>(that is, country)</i> of nationality:	State <i>(that is, country)</i> of residence:
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.	

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Sheet No. ...3...

Box No. V DESIGNATION OF STATES

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

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

Regional Patent

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

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

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

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

- | | | |
|--------------------------------|--------------------------------|--------------------------------|
| ☐ | ☐ | ☐ |
| ☐ | ☐ | ☐ |

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

See Notes to the request form

Box No. IX CHECK LIST; LANGUAGE OF FILING		
This international application contains:		This international application is accompanied by the following item(s) (mark the applicable check-boxes below and indicate in right column the number of each item):
(a) the following number of sheets in paper form:		
request (including declaration sheets)	5	1. ☒ fee calculation sheet : 1
description (excluding sequence listing part)	24	2. ☒ original separate power of attorney : 1
claims	4	3. ☐ original general power of attorney :
abstract	1	4. ☐ copy of general power of attorney; reference number, if any: :
drawings		5. ☐ statement explaining lack of signature :
Sub-total number of sheets :	34	6. ☒ priority document(s) identified in Box No. VI as item(s): : 1
sequence listing part of description (actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (b) below)		7. ☐ translation of international application into (language): :
Total number of sheets :	34	8. ☐ separate indications concerning deposited microorganism or other biological material :
(b) sequence listing part of description filed in computer readable form		9. ☐ sequence listing in computer readable form (indicate also type and number of carriers (diskette, CD-ROM, CD-R or other)) :
(i) ☐ only (under Section 801(a)(i))		(i) ☐ copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application) :
(ii) ☐ in addition to being filed in paper form (under Section 801(a)(ii))		(ii) ☐ (only where check-box (b)(i) or (b)(ii) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Rule 13ter :
Type and number of carriers (diskette, CD-ROM, CD-R or other) on which the sequence listing part is contained (additional copies to be indicated under item 9(ii), in right column):		(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left column :
		10. ☐ other (specify): :
Figure of the drawings which should accompany the abstract:		Language of filing of the international application: English
Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE		
Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).		
BOEHRINGER INGELHEIM PHARMA KG		
I.V. 	I.A. 	
Dr. Rothemel	Dr. Nühring	

For receiving Office use only	
1. Date of actual receipt of the purported international application:	2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority (if two or more are competent): ISA /	6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only
Date of receipt of the record copy by the International Bureau:

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PCT/EP02/08993

Wolk

Eintrag in CD Patents	
04. Juni 2003	
Erreichte	PCT erledigt

PATENT COOPERATION TREATY

ERFASST

From the INTERNATIONAL BUREAU

NOTIFICATION OF THE RECORDING OF A CHANGE

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

To:

BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG
Binger Strasse 173
55216 Ingelheim am Rhein
Germany

INGEGANGEN
05. Juni 2003
Erlosg.

Date of mailing (day/month/year) 23 May 2003 (23.05.03)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference 1/1248	
International application No. PCT/EP02/08993	International filing date (day/month/year) 10 August 2002 (10.08.02)

1. The following indications appeared on record concerning:

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

Name and Address BOEHRINGER INGELHEIM PHARMA KG Binger Strasse 173 55216 Ingelheim am Rhein Germany	State of Nationality DE	State of Residence DE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

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

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

Name and Address BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG Binger Strasse 173 55216 Ingelheim am Rhein Germany	State of Nationality DE	State of Residence DE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

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

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

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 740.14.35	Authorized officer Brigitte WYSS Telephone No. (41-22) 338 8388
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WO 03/015787
PCT/EP02/008993

PATENT COOPERATION TREATY

EINGEGANGEN
PCT 19. März 2003
Erled.

From the INTERNATIONAL BUREAU

EINGEGANGEN
13. März 2003
Erled.

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

To:

BOEHRINGER INGELHEIM PHARMA KG
Binger Strasse Eingang CD Patents
55216 Ingelheim am Rhein
ALLEMAGNE 12. März 2003

(PCT Rule 47.1(c), first sentence)

Date of mailing (day/month/year) 27 February 2003 (27.02.03)		SB gesehen erledigt 12/13	
Applicant's or agent's file reference 1/1248		IMPORTANT NOTICE	
International application No. PCT/EP02/008993	International filing date (day/month/year) 10 August 2002 (10.08.02)	Priority date (day/month/year) 17 August 2001 (17.08.01)	
Applicant BOEHRINGER INGELHEIM PHARMA KG			

ERFASST

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

KP, KR, US

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

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

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

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

3. Enclosed with this notice is a copy of the international application as published by the International Bureau on 27 February 2003 (27.02.03) under No. WO 03/015787.

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

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

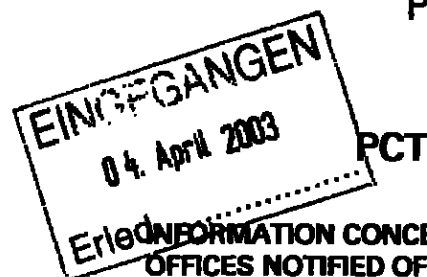
In practice, time limits other than the 30-month time limit will continue to apply, for various periods of time, in respect of certain designated or elected Offices. For regular updates on the applicable time limits (20, 21, 30 or 31 months, or other time limit), Office by Office, refer to the *PCT Gazette*,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

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

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

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Judith Zahra
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.91.11

PATENT COOPERATION TREATY



INFORMATION CONCERNING ELECTED
OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

From the INTERNATIONAL BUREAU

To:

BOEHRINGER INGELHEIM PHARMA KG
Binger Strasse 173 Eingang CD Patents
55216 Ingelheim am Rhein
Germany

03 April 2003

SB gesehen erledigt
N/L

IMPORTANT INFORMATION

Date of mailing (day/month/year) 18 March 2003 (18.03.03)		
Applicant's or agent's file reference 1/1248		
International application No. PCT/EP02/08993	International filing date (day/month/year) 10 August 2002 (10.08.02)	Priority date (day/month/year) 17 August 2001 (17.08.01)
Applicant BOEHRINGER INGELHEIM PHARMA KG et al		

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

EP : AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR
National : AU, BG, CA, CN, DE, GB, IL, JP, KP, KR, MN, NO, PL, RO, RU, SK, US

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

AP : GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW
EA : AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
OA : BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
National : AE, AG, AL, AM, AT, AZ, BA, BB, BR, BY, BZ, CH, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, ES, FI, GD, GE, GH, GM, HR, HU, ID, IN, IS, KE, KG, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MW, MX, MZ, NZ, OM, PH, PT, SD, SE, SG, SI, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW

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

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

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

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer: - Brigitte WYSS
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338 8386

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: BOEHRINGER INGELHEIM PHARMA KG 55216 Ingelheim am Rhein ALLEMAGNE	Eingang CD Patents 11 Nov. 2003	EINGEGANGEN 13 Nov. 2003 Erl. PCT NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT (PCT Rule 71.1)
		Date of mailing (day/month/year) 10.11.2003
Applicant's or agent's file reference 1/1248		IMPORTANT NOTIFICATION
International application No. PCT/EP02/08993	International filing date (day/month/year) 10.08.2002	Priority date (day/month/year) 17.08.2001
Applicant BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG et al.		

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

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

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

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

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

Name and mailing address of the international preliminary examining authority: European Patent Office D-80299 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Ladumer, Y Tel. +49 89 2399-7913
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PATENT COOPERATION TREATY
PCT
INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 1/248		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)	
International application No. PCT/EP02/08993	International filing date (day/month/year) 10.08.2002	Priority date (day/month/year) 17.08.2001	
International Patent Classification (IPC) or both national classification and IPC A61K31/517			
Applicant BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG et al.			
1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of 5 sheets, including this cover sheet. ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT). These annexes consist of a total of sheets.			
3. This report contains indications relating to the following items: I ☒ Basis of the opinion II ☐ Priority III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV ☐ Lack of unity of invention V ☒ Reasoned statement under Rule 66.2(a)(II) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI ☐ Certain documents cited VII ☐ Certain defects in the international application VIII ☐ Certain observations on the international application			
Date of submission of the demand 13.02.2003		Date of completion of this report 10.11.2003	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80289 Munich Tel. +49 89 2399 - 0 Tlx 523656 epmu d Fax: +49 89 2399 - 4465		Authorized Officer Herrera, S Telephone No. +49 89 2399-8464 	

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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/EP02/08993**

I. Basis of the report

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

Description, Pages

1-24 as originally filed

Claims, Numbers

1-18 as originally filed

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

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

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

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

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

4. The amendments have resulted in the cancellation of:

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

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

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

6. Additional observations, if necessary:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/EP02/08993**

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

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

- ☐ the entire international application,
- ☒ claims Nos. 1-6
because:
 - ☒ the said international application, or the said claims Nos. 1-6 relate to the following subject matter which does not require an international preliminary examination (specify):
see separate sheet
 - ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
 - ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
 - ☐ no international search report has been established for the said claims Nos.

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

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

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

1. Statement

Novelty (N)	Yes: Claims	1-16
	No: Claims	
Inventive step (IS)	Yes: Claims	5-10, 14, 15
	No: Claims	1-4, 11-13, 16
Industrial applicability (IA)	Yes: Claims	7-16
	No: Claims	

2. Citations and explanations

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP02/08993

Section III

Claims 1-6 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Section V

1. Reference is made to the following documents:

D1: DOODS H ET AL: 'PHARMACOLOGICAL PROFILE OF BIBN4096BS, THE FIRST SELECTIVE SMALL MOLECULE CGRP ANTAGONIST' BRITISH JOURNAL OF PHARMACOLOGY, BASINGSTOKE, HANTS, GB, vol. 129, no. 3, 2000, pages 420-423, XP000992559 ISSN: 0007-1188

D2: FERRARI M D ET AL: 'Oral triptans (serotonin 5-HT_{1B/1D} agonists) in acute migraine treatment: a meta-analysis of 53 trials' LANCET, XX, XX, vol. 358, no. 9294, 17 November 2001 (2001-11-17), pages 1668-1675, XP004323637 ISSN: 0140-6736

D3: DATABASE MEDLINE [Online] 15 November 1993 (1993-11-15)
HOERNECKE R ET AL: '[Treatment of migraine attacks: combination of dihydroergotamine tartrate and paracetamol in comparison with individual drugs and placebo]' Database accession no. NLM8295604 XP002199881 & MEDIZINISCHE KLINIK (MUNICH, GERMANY: 1983) GERMANY 15 NOV 1993, vol. 88, no. 11, 15 November 1993 (1993-11-15), pages 642-648, ISSN: 0723-5003

D4: DATABASE MEDLINE [Online] January 1992 (1992-01) SAADAH H A: 'Abortive headache therapy with intramuscular dihydroergotamine.' Database accession no. NLM1555927 XP002216638 & HEADACHE. UNITED STATES JAN 1992, vol. 32, no. 1, January 1992 (1992-01), pages 18-20, ISSN: 0017-8748

2. The subject-matter of the present claims can be considered novel in that the prior art does not disclose combination of BIBN4096 with other anti-migraine drugs (Art 33 (2) PCT).
3. It is however known to use BIBN4096 in the treatment of migraine and therefore it is prima facie obvious to combine it with other anti-migraine drugs.

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INTERNATIONAL PRELIMINARY

International application No. PCT/EP02/08993

EXAMINATION REPORT - SEPARATE SHEET

For the combination with sumatriptan, zolmitriptan and dihydroergotamine the applicant has shown a synergistic affect so that an inventive step can be acknowledged for claims 5-10, 14 and 15.

However, because of the nature of a synergistic effect, they cannot be transferred to other combinations so that an inventive step for the subject-matter of claims 1-4, 11-13 and 16 cannot be acknowledged (Art 33 (3) PCT).

Traducción

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

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Referencia del expediente del agente o solicitante 1/1248	PARA ACTUACIONES ADICIONALES Ver notificación de Transmisión del Reporte de Examen Preliminar (Formato PCT/IPEA416)	
Solicitud Internacional No. PCT/EP02/08993	Fecha de presentación Internacional (día/mes/año) 10 de Agosto de 2002	Fecha de prioridad (día/mes/año) 17 de Agosto de 2001
Clasificación Internacional de Patentes (IPC) o clasificación nacional e IPC A61K 31/517		
Solicitante BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG Et al.		

- Este informe de examen preliminar Internacional ha sido preparado por esta Administración encargada del Examen Preliminar Internacional y se envía al solicitante en concordancia con el artículo 36.
- Este INFORME consta de una total de 5 hojas, incluyendo la portada
☐ Este informe también se acompaña de ANEXOS, esto es documentos de la descripción, reivindicaciones y/o dibujos que han sido corregidos y que son la base de este informe y/o documentos que contienen rectificaciones realizadas ante esta Administración (Ver Regla 70.16 y Sección 807 de las Instrucciones Administrativas según el PCT)

Estos anexos constan de un total de _____ hojas.

- Este informe contiene indicaciones relativas a los siguientes aspectos:

- | | | |
|------|-------------------------------------|--|
| I | ☒ | Fundamentos del Informe |
| II | ☐ | Prioridad |
| III | ☒ | No se establece concepto relativo a la novedad, nivel inventivo y aplicación Industrial |
| IV | ☐ | Carencia de unidad de la invención |
| V | ☒ | Declaración razonada según el artículo 35(2), en relación con la novedad, nivel inventivo o aplicación industrial; citaciones y explicaciones que soportan dicha declaración |
| VI | ☐ | Ciertos documentos citados |
| VII | ☐ | Ciertos defectos de la solicitud internacional |
| VIII | ☐ | Ciertas observaciones respecto a la solicitud Internacional |

Fecha de presentación de la demanda Febrero 13 de 2003	Fecha de terminación de este reporte Noviembre 10 de 2003
Nombre y dirección de correo de la autoridad encargada del examen preliminar  Oficina Europea de Patentes D-80299 Munich Tel. +49 89 2399 - 0 Tlx: 523656 epmu d Fax: +49 89 2399 - 4465	Funcionario Autorizado Herrera, S Teléfono No. +49 89 2399-8464

Formato PCT/IPEA409 (portada) (julio 1998)

I. Base del Informe

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

La descripción:

páginas 1-24, como se presentaron originalmente

Las reivindicaciones:

Números 1-16, como se presentaron originalmente

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

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

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

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

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

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

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

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

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

6. Observaciones adicionales, si es necesario:

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

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

- ☐ la solicitud Internacional completa
☒ las reivindicaciones Nos. 1-6.

Porque

- ☒ la solicitud Internacional, o las mencionadas reivindicaciones Nos. 1-6 se relacionan con los siguientes objetos, los cuales no requieren examen preliminar Internacional (*especifique*):

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- ☐ la descripción, las reivindicaciones o los dibujos (*Indique los elementos particulares abajo*) o las mencionadas reivindicaciones Nos. _____ son demasiado confusas que no se puede formar ninguna opinión significativa (*especifique*):

- ☐ la descripción, o las mencionadas reivindicaciones Nos. _____ no están adecuadamente soportadas por la descripción que no se puede formar ninguna opinión significativa.

- ☐ no se ha establecido un reporte de búsqueda para las mencionadas reivindicaciones Nos.

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

- ☐ El formato escrito no ha sido suministrado o no cumple con los estándares.

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

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

1. Declaración

Novedad (N)	SI:	Reivindicaciones	1-16
	NO:	Reivindicaciones	
Nivel inventivo (NI)	SI:	Reivindicaciones	5-10, 14, 15
	NO:	Reivindicaciones	1-4, 11-13, 16
Aplicación Industrial (AI)	SI:	Reivindicaciones	7-16
	NO:	Reivindicaciones	

2. Citas y explicaciones (Regla 70.7)

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SECCIÓN III

Esta Autoridad considera que el objeto de las reivindicaciones 1 a 6 se encuentra cubierto por lo provisto en la Regla 67.1 (iv) PCT. Consecuentemente, no podrá formularse una opinión con respecto a la aplicabilidad Industrial del objeto de dichas reivindicaciones. (Artículo 34(4)(a)(i)PCT)

SECCIÓN V

1. Se hace referencia a los siguientes documentos:

D1: DOODS H ET AL: "Perfil farmacológico de bibrn4096bs, la primera molécula pequeña selectiva antagonista cgrp" BRITISH JOURNAL OF PHARMACOLOGY, BASINGSTOKE, HANTS, GB, VOL. 129, NO. 3, 2000, PAGES 420-423, XP000992559 ISSN 0007-1188.

D2: FERRARI M D ET AL: "Triptanos orales (agonistas de serotonina 5-HT1B/1D) en el tratamiento de la migraña aguda: un metaanálisis de 53 ensayos" LANCET XX, XX, vol 358, no. 9294, 17 de Noviembre de 2001 (2001-11-17), páginas 1668-1675, XP004323637 ISSN: 0140-6736.

D3: DATABASE MEDLINE [Online] 15 de Noviembre de 1993 (1993-11-15) HOERNECKE R ET AL: "[Tratamiento de ataques de migraña: combinación de tartrato de dihidroergotamina y paracetamol en comparación con los fármacos individuales y placebo]" Acceso de base de datos no. NLM8295604 XP002199881 & MEDIZINSCHES KLINIK (MUNICH, GERMANY: 1983) Alemania 15 de Noviembre de 1993 81993-11-15), páginas 642-648, SIN: 0723-5003.

D4: DATABASE MEDLINE [Online] Enero 1992 (1992-01) SAADAH H A: "Terapia abortiva para dolor de cabeza con dihidroergotamina intramuscular". Acceso a la base de datos no. NLM1555927 XP002216638 & HEADACHE. Estados Unidos Enero 1992, vol. 32, no. 1, Enero 1992 (1992-01), páginas 18-20, SIN 0017-8748.

2. El objeto de las presentes reivindicaciones puede ser considerado novedoso ya que el arte previo no divulga la combinación de BIBN4096 con otros fármacos antimigrañosos (Artículo 33 (2)PCT).
3. Sin embargo es conocido el uso de BIBN4096 en el tratamiento de la migraña y por esto a primera vista es obvio combinarlo con otros fármacos antimigrañosos.

Para la combinación de sumatriptan, zolmitriptan y dihidroergotamina, el solicitante ha demostrado un efecto sinérgico de tal forma que el nivel inventivo puede alcanzarse para las reivindicaciones 5-10, 14 y 15.

Sin embargo, debido a la naturaleza de el efecto sinérgico, este no puede ser atribuido a otras combinaciones de tal forma que no puede alcanzarse el nivel inventivo del objeto de las reivindicaciones 1-4, 11-13 y 16. (Artículo 33(3)PCT)

Uso de BIBN4096 en combinación con otros fármacos antimigrañosos para el tratamiento de migraña

5

Campo de la Invención

La migraña es uno de los trastornos neurológicos más comunes, que implica ataques periódicos de cefalea y náuseas así como otros síntomas muy diversos. Aunque se ha realizado un progreso considerable, todavía no se entiende la patofisiología de la migraña. Sin embargo, varias observaciones apuntan a la implicación del péptido relacionado con el gen de la calcitonina (CGRP). La cefalea migrañosa implica la activación del sistema trigeminal y la dilatación de los vasos sanguíneos craneales. El CGRP está localizado en las neuronas, de los ganglios trigeminales, y los niveles de CGRP se elevan durante un ataque de migraña, causando presumiblemente la vasodilatación observada. Por consiguiente, es concebible que la inhibición de la dilatación de los vasos craneales evocada por CGRP pueda proporcionar un nuevo tratamiento para la cefalea migrañosa.

Unos fármacos antimigrañosos muy utilizados son los llamados "triptanes", p.ej. sumatriptán y zolmitriptán. Estos compuestos incitan sus efectos antimigrañosos debido a sus propiedades vasoconstrictoras y presumiblemente a su inhibición de la liberación del neuropeptido denominado péptido relacionado con el gen de la calcitonina (CGRP, por sus siglas en inglés) (Ferrari, M. D., Saxena, P. R. (1995), 5-HT₁ receptors in migraña pathophysiology and treatment, *Eur. J. Neurology*, 2, 5-21; Johnson, K. W., Phebus, L. A., Cohen, M. L. (1998), Serotonin in migraña: The roles, animal models and emerging therapies, *Progress in Drug Research*, Vol. 51, 220-244), cuyos niveles se supone que se incrementan durante un ataque de migraña (Edvinsson, L., Goadsby, P. J. (1994), Neuropeptides in migraña and cluster cefaleas, *Cephalgia*, 14(5), 320-327). Una estrategia completamente nueva para tratar la migraña es el uso de antagonistas de CGRP (Doods, H., Hallermayer, G., Wu, D., Entzeroth, M., Rudolf, K., Engel, W., Eberlein, W. (2000), Pharmacological profile of BIBN4096BS, the first selective small molecule CGRP antagonist, *Br. J. Pharmacol.*, 129, 420-423).

Antecedentes de la Invención

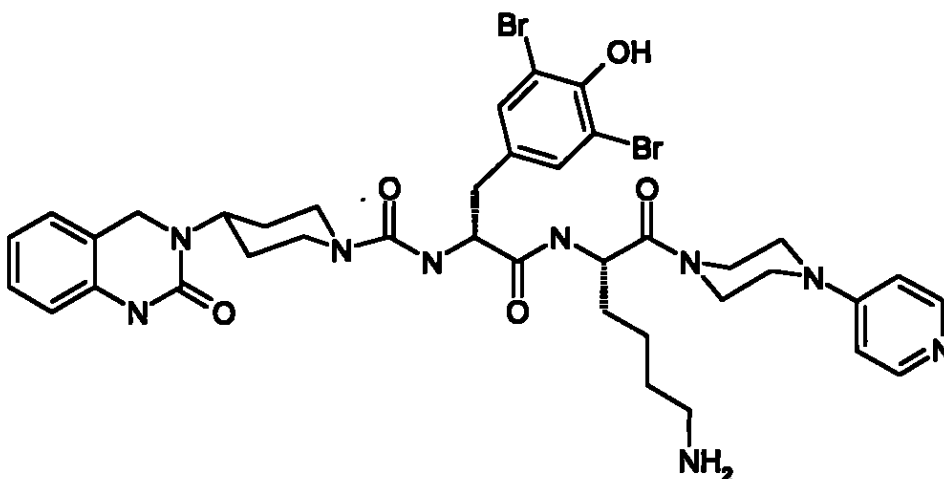
El documento WO 98/11128 describe aminoácidos modificados que tienen propiedades antagonistas de CGRP, su uso y métodos para su preparación así como

su uso para la producción y purificación de anticuerpos y como compuestos marcados en ensayos RIA y ELISA y como agentes auxiliares diagnósticos o analíticos en la búsqueda de neurotransmisores. En vista de sus propiedades farmacológicas, los aminoácidos modificados son por lo tanto adecuados para tratamiento agudo y profiláctico de las cefaleas, particularmente de la migraña y las cefaleas en racimo.

Compendio de la Invención

Se ha encontrado inesperadamente que en un modelo que se considera predictivo de los efectos antimigrañosos de los fármacos, la combinación de dos fármacos con un modo completamente diferente de acción, a saber un agonista de 5-HT_{1B/1D} o un alcaloide del ergot y el antagonista de CGRP descrito en el documento WO 98/11128 A1, a saber

A = 1-[N²-[3,5-Dibromo-N-[[4-(3,4-dihidro-2(1H)-oxoquinazolin-3-il)-1-piperidinil]-carbonil]-D-tirosil]-L-Isl]-4-(4-piridinil)-piperazina [BIBN4096BS],



da como resultado un efecto mejor altamente significativo si se compara con el efecto de un fármaco a solas.

Descripción detallada de la Invención

Según un primer aspecto, la presente invención proporciona un método de tratamiento o prevención de indicaciones seleccionadas del grupo formado por cefaleas, migraña y cefaleas en racimo, cuyo método comprende la administración conjunta de una cantidad terapéuticamente eficaz de BIBN4096BS o una sal fisiológicamente aceptable del mismo y una cantidad terapéuticamente eficaz de otro fármaco anti-

gráfico activo (A) a una persona que tiene necesidad de dicho tratamiento.

Para este propósito, el fármaco (A) se puede seleccionar del grupo formado por antieméticos, procinéticos, neurolepticos, antidepresivos, antagonistas de neuroquinina, anti-convulsivos, antagonistas del receptor H1 de histamina, antimuscarínicos, β -bloqueantes, α -agonistas y α -antagonistas, alcaloides del ergot, analgésicos suaves, antiflogísticos no esteroideos, corticosteroides, antagonistas del calcio y agonistas de 5-HT_{1B/1D}.

Un antiflogístico no esteroideo se puede seleccionar del grupo formado por acetofenaco, acetaminofeno, ácido acetilsalicílico, azatoprina, celecoxib, diclofenaco, diflunisal, fenbufeno, fenoprofeno, flurbiprofeno, ibuprofeno, indometacina, ketoprofeno, leflunomida, lornoxicam, ácido mefenámico, meloxicam, naproxeno, fenilbutazona, piroxicam, sulfasalazina, zomepiraco o las sales farmacéuticamente aceptables de los mismos,

como agonistas de 5-HT_{1B/1D} se pueden utilizar, por ejemplo, almotriptán, avitriptán, eletriptán, frovatriptán, naratriptán, rizatriptán, sumatriptán o zolmitriptán o las sales farmacéuticamente aceptables de los mismos y

alcaloides adecuados del ergot son, por ejemplo, ergotamina y dihidroergotamina.

Otras sustancias activas adicionales que se pueden considerar para las combinaciones mencionadas anteriormente como el componente farmacológico (A) incluyen, por ejemplo, metoclopramida, domperidona, difenhidramina, ciclizina, prometazina, clorpromazina, dexametasona, flunarizina, dextropropoxifeno, meperidina, propranolol, nadolol, atenolol, clonidina, indoramina, carbamazepina, fenitoína, valproato, amitriptilina, lidocaína o diltiazem.

Como una realización preferida en el método de acuerdo con la invención, el fármaco (A) se selecciona del grupo formado por los alcaloides del ergot y los agonistas de 5-HT_{1B/1D}, especialmente preferidos son dihidroergotamina, sumatriptán y zolmitriptán, el más preferido es sumatriptán o sus sales fisiológicamente aceptables.

Como una realización preferida adicional en el método de acuerdo con la invención, el fármaco (A) se selecciona del grupo formado por antiflogísticos no esteroideos, es especialmente preferido meloxicam o sus sales fisiológicamente aceptables.

La dosificación para el fármaco antimigrañoso combinado (A) es apropiadamente 1/50 de la dosis más baja recomendada normalmente hasta 1/1 de la dosificación recomendada normalmente, preferiblemente 1/50 a 1/6 y más preferiblemente

1/20 a 1/10, por vía oral, nasal, subcutánea o intravenosa. La dosis normalmente recomendada para el fármaco antimigrañoso combinado (A) deberá interpretarse como la dosis descrita en Rote Liste Win® 2001/I, Editio Cantor Verlag Aulendorf.

5 De acuerdo con la invención, BIBN4096BS o una sal fisiológicamente aceptable del mismo, se puede administrar por vía intravenosa o subcutánea en una dosificación de 0,0001 a 3 mg/kg de peso corporal o por vía oral, nasal o inhalativa en una dosificación de 0,1 a 10 mg/kg de peso corporal, una, dos o tres veces al día, en combinación con

10 sumatriptán o una sal fisiológicamente aceptable del mismo, que se puede administrar por vía oral en una dosificación de 0,03 a 1,43 mg/kg de peso corporal, una, dos o tres veces al día, o

por vía intravenosa o subcutánea en una dosificación de 0,002 a 0,09 mg/kg de peso corporal, una o dos veces al día, o

15 por vía rectal en una dosificación de 0,007 a 0,36 mg/kg de peso corporal, una o dos veces al día, o

por vía nasal en una dosificación de 0,006 a 0,29 mg/kg de peso corporal, una o dos veces al día, o en combinación con

20 zolmitriptán o una sal fisiológicamente aceptable del mismo, que se puede administrar por vía oral en una dosificación de 0,0007 a 0,036 mg/kg de peso corporal, una o dos veces al día, o

en combinación con dihidroergotamina o una sal fisiológicamente aceptable de la misma, que se puede administrar por vía oral en una dosificación de 0,001 a 0,07 mg/kg de peso corporal, una o dos veces al día, o en combinación con

25 meloxicam o una sal fisiológicamente aceptable del mismo, que se puede administrar por vía oral en una dosificación de 0,004 a 0,21 mg/kg de peso corporal, una vez al día.

30 En una realización preferida de la invención, BIBN4096BS o una sal fisiológicamente aceptable del mismo, se puede administrar por vía intravenosa o subcutánea en una dosificación de 0,0001 a 3 mg/kg de peso corporal o por vía oral, nasal o inhalativa en una dosificación de 0,1 a 10 mg/kg de peso corporal, una, dos o tres veces al día, en combinación con

sumatriptán o una sal farmacéuticamente aceptable del mismo, que se puede administrar por vía oral en una dosificación de 0,03 a 0,24 mg/kg de peso corporal, una, dos o tres veces al día, o

35 por vía intravenosa o subcutánea en una dosificación de 0,002 a 0,015 mg/kg

- de peso corporal, una o dos veces al día, o
- por vía rectal en una dosificación de 0,007 a 0,06 mg/kg de peso corporal, una o dos veces al día, o
- por vía nasal en una dosificación de 0,006 a 0,048 mg/kg de peso corporal,
- 5 una o dos veces al día, o en combinación con
- zolmitriptán o una sal fisiológicamente aceptable del mismo, que se puede administrar por vía oral en una dosificación de 0,0007 a 0,006 mg/kg de peso corporal, una o dos veces al día, o
- en combinación con dihidroergotamina o una sal fisiológicamente aceptable
- 10 de la misma, que se puede administrar por vía oral en una dosificación de 0,001 a 0,01 mg/kg de peso corporal, una o dos veces al día, o
- en combinación con meloxicam o una sal fisiológicamente aceptable del mismo, que se puede administrar por vía oral en una dosificación de 0,004 a 0,036 mg/kg de peso corporal, una vez al día.
- 15 En una realización más preferida de la invención, BIBN4096BS o una sal fisiológicamente aceptable del mismo, se puede administrar por vía intravenosa o subcutánea en una dosificación de 0,0001 a 3 mg/kg de peso corporal o por vía oral, nasal o inhalativa en una dosificación de 0,1 a 10 mg/kg de peso corporal una, dos o tres veces al día, en combinación con
- 20 sumatriptán o una sal fisiológicamente aceptable del mismo, que se puede administrar por vía oral en una dosificación de 0,075 a 1,43 mg/kg de peso corporal, una, dos o tres veces al día, o
- por vía intravenosa o subcutánea en una dosificación de 0,005 a 0,009 mg/kg de peso corporal, una o dos veces al día, o
- 25 por vía rectal en una dosificación de 0,0175 a 0,036 mg/kg de peso corporal, una o dos veces al día, o
- por vía nasal en una dosificación de 0,015 a 0,029 mg/kg de peso corporal, una o dos veces al día, o en combinación con
- zolmitriptán o una sal fisiológicamente aceptable del mismo, que se puede
- 30 administrar por vía oral en una dosificación de 0,00175 a 0,0036 mg/kg de peso corporal, una o dos veces al día, o
- en combinación con dihidroergotamina o una sal fisiológicamente aceptable de la misma, que se puede administrar por vía oral en una dosificación de 0,0025 a 0,007 mg/kg de peso corporal, una o dos veces al día, o
- 35 en combinación con meloxicam o una sal fisiológicamente aceptable del

mismo, que se puede administrar por vía oral en una dosificación de 0,01 a 0,02 mg/kg de peso corporal, una vez al día.

La presente invención proporciona, como segundo aspecto, una composición farmacéutica para tratar o prevenir cefalea, migraña o cefaleas en racimo, que comprende una cantidad terapéuticamente eficaz de BIBN4096BS o un sal del mismo fisiológicamente aceptable y un fármaco antimigrañoso (A) seleccionado del grupo formado por sumatriptán, zolmitriptán y dihidroergotamina o una de sus sales fisiológicamente aceptables como una preparación de combinación para administración simultánea o secuencial.

Una composición farmacéutica de acuerdo con la invención puede comprender una sola unidad de dosificación de 0,1 a 10 mg de BIBN4096BS y una sola unidad de dosificación de 1 a 100 mg de sumatriptán o una sola unidad de dosificación de 0,1 a 2,5 mg de zolmitriptán o una sola unidad de dosificación de 0,1 a 5 mg de dihidroergotamina o una sola unidad de dosificación de 7,5 a 15 mg de meloxicam.

Todas las dosis o unidades de dosificación de una sal fisiológicamente aceptable de un compuesto activo mencionado aquí anteriormente deberá interpretarse como la dosis o dosificación del propio compuesto activo.

Además, una composición farmacéutica de acuerdo con la invención puede ser un kit de partes para tratar o prevenir cefalea, migraña o cefaleas en racimo, kit que comprende

- (a) un primer envase que contiene una composición farmacéutica que comprende una cantidad terapéuticamente eficaz de BIBN4096BS o una sal fisiológicamente aceptable del mismo y uno o más diluyentes y/o vehículos farmacéuticamente aceptables; y
- (b) un segundo envase que contiene una composición farmacéutica que comprende sumatriptán, zolmitriptán o dihidroergotamina o una de sus sales fisiológicamente aceptables y uno o más diluyentes y/o vehículos farmacéuticamente aceptables.

Un kit de partes preferido comprende sumatriptán en el segundo envase.

Un tercer aspecto de la presente invención es el uso de BIBN4096BS o una sal del mismo fisiológicamente aceptable en combinación con otro fármaco antimigrañoso activo (A) para la fabricación de una composición farmacéutica para tratar o prevenir cefalea, migraña o cefaleas en racimo. El fármaco (A) y las realizaciones preferidas del mismo, así como sus composiciones farmacéuticas, se han mencionado aquí

anteriormente bajo el primer y segundo aspectos de la invención. Lo más preferido en relación con todos los aspectos de la invención es la combinación de BIBN4096BS con sumatriptán o una de sus sales fisiológicamente aceptables.

5 Varios de los componentes farmacológicos (A) mencionados aquí anteriormente ya están en el mercado, p.ej., sumatriptán se vende bajo el nombre comercial Imigran®, zolmitriptán se vende bajo el nombre comercial ascotop® y dihidroergotamina y sus sales farmacéuticamente aceptables, se venden bajo el nombre comercial agit®.

10 El BIBN4096BS se puede administrar, por ejemplo, utilizando las formulaciones farmacéuticas descritas en el documento WO 98/11128 o utilizando una de las siguientes formulaciones farmacéuticas:

- cápsulas para inhalación de polvo, que contienen 1 mg de sustancia activa,
- 15 solución inhalable para nebulizadores, que contiene 1 mg de sustancia activa,
- aerosol dosificador accionado por un gas propelente, que contiene 1 mg de sustancia activa,
- 20 spray nasal, que contiene 1 mg de sustancia activa,
- comprimidos, que contienen 20 mg de sustancia activa,
- 25 cápsulas, que contienen 20 mg de sustancia activa,
- solución acuosa para aplicación nasal, que contiene 10 mg de sustancia activa,
- solución acuosa para aplicación nasal, que contiene 5 mg de sustancia activa, o
- 30 suspensión para aplicación nasal, que contiene 20 mg de sustancia activa.

Ejemplo 1

35 Con objeto de examinar la actividad farmacológica de las combinaciones de acuerdo con la invención, se han llevado a cabo los siguientes experimentos:

Medición del flujo sanguíneo cutáneo facial

El flujo sanguíneo cutáneo facial se midió por un método modificado descrito por Escott et al. (Escott, K. J., Beattie, D. T., Connor, H. E., Brain, S. D. (1995), Trigeminal ganglion stimulation increases facial skin blood flow in the rat: a major role for calcitonin gene-related peptide, *Brain Research*, 669(1), 93-99). Se anestesiaron ratas wistar machos mantenidas en ayunas (raza CHbb:THOM, 280-320 g) con pento-
 5 barbitona sódica (Inicialmente con 60 mg/kg i.p. y mantenidas a lo largo de todo el experimento con una infusión intraperitoneal de 30 mg/kg/h a través de una aguja de calibre 23 utilizando una solución de 10 mg/ml). Ambos lados de la zona bucal de la
 10 piel facial se afeitaron y depilaron con una crema depilatoria comercial (Pilca, Schwarzkopf & Henkel, 40551 Düsseldorf, Alemania). Se canuló la tráquea y se sometieron a ventilación artificial los animales (80 inspiraciones/mln) con aire atmosférico enriquecido en oxígeno. Se mantuvo la temperatura corporal a 37°C mediante un le-
 15 cho calefactor automático. Se canularon la arteria femoral izquierda y la vena femoral izquierda para la medición continua de la presión sanguínea arterial y la administración intravenosa de los compuestos de ensayo, respectivamente. Se estableció un bloqueo neuromuscular por administración intravenosa de bromuro de pancuronio (1
 20 mg/kg/0,5ml, 5 mln antes de cada estimulación eléctrica). La frecuencia cardíaca se obtenía a partir de la señal de la presión sanguínea. La presión sanguínea y la frecuencia cardíaca eran vigiladas continuamente durante el curso del experimento para estimar el nivel de anestesia y vigilar los efectos cardiovasculares de los fármacos utilizados en este estudio.

Se pusieron los animales en un armazón esterotáxico y se hizo una incisión longitudinal en el cuero cabelludo. Se taladró un pequeño agujero en el cráneo (a la
 25 izquierda o a la derecha) y se introdujo un electrodo bipolar (Rhodes SNEX-100 suministrado por David Kopf Instruments, Tujunga, 91042 California, EE.UU.) utilizando un micromanipulador, en el ganglio trigeminal (a una distancia de 0,32 cm dorsal a bregma, una distancia $\pm$ 0,30 cm lateral desde la línea media y 0,95 cm debajo de la superficie dural). La posición de los electrodos en los ganglios trigeminales fue verificada
 30 visualmente al final de cada experimento tras la extirpación del cerebro. Se estimuló el ganglio trigeminal a 10 Hz, 1 mA, 1 ms durante 30 segundos utilizando un estimulador suministrado por Hugo Sachs Elektronik (79232 March-Hugstetten, Alemania). Se midieron los cambios en el flujo sanguíneo microvascular en la piel facial utilizando fluo-
 35 metría Láser Doppler con un sistema láser Doppler Periflux (PeriFLUX 4001, longitud de onda 780 nm; tiempo constante 3 s, Perimed AB, Järfälla, S-17526, Suecia). Se

situaron sondas láser Doppler normales (SONDA 408) a cada lado de la cara a una distancia de aproximadamente 0,5 cm debajo del centro del ojo, un área innervada por la rama maxilar (V2) del nervio trigeminal. Se midieron los cambios de flujo sanguíneo como flujo en unidades arbitrarias y se expresa como área bajo la curva de flujo (mm²) de acuerdo con Escott et al. (1995).

Protocolo experimental

Después de 30 min de equilibración, los animales se sometieron a tres períodos de estimulación eléctrica, separados por un intervalo de 30 min. La primera estimulación se utilizó como un control para las subsiguientes estimulaciones. 5 min antes de la segunda estimulación, se administraron intravenosamente solución salina, compuesto individual o la combinación.

Los resultados se dan en la Tabla 1 siguiente. Dichos resultados indican que la potencia mejorada de la combinación de agonistas de 5-HT_{1B/1D} u otros fármacos antimigrañosos en general con un antagonista de CGRP permitiría mayor eficacia, permitiría dosis más bajas de cada compuesto para obtener una eficacia similar con menos efectos secundarios y la adición de los mecanismos podría dar como resultado menor recurrencia de las cefaleas.

Tabla 1: Efecto de BIBN4096BS en combinación con otros fármacos antimigrañosos sobre la vasodilatación cutánea facial inducida por la estimulación eléctrica de los ganglios trigeminales en la rata.

Tratamiento	% de estimulación del trigémino	n	% de Inhibición comparado con valor control
Solución salina (control)	82,7 ± 4,4	11	-
BIBN 4096 BS (0,03 mg/kg)	60,3 ± 5,1	8	27.1
Sumatriptán (1,0 mg/kg)	68,8 ± 6,8	7	16,8
BIBN 4096 BS + sumatriptán (0,03 mg + 1,0 mg)/kg	26,6 ± 5,4 ^a	6	67,8
Zolmitriptán (0,1 mg/kg)	55,6 ± 4,8	6	32,8
BIBN 4096 BS + Zolmitriptán (0,03 mg + 0,1 mg)/kg	27,3 ± 6,0 ^a	6	67,0
DHE (0,1 mg/kg)	60,4 ± 4,1	6	27,0
BIBN 4096 BS + DHE (0,03 mg + 0,1 mg)/kg	20,9 ± 3,1 ^c	6	74,7

DHE = Dihidroergotamina

^a significativo, p < 0,001, comparado con sumatriptán

^b significativo, p < 0,01, comparado con zolmitriptán

^c significativo, p < 0,001, comparado con DHE

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Los Ejemplos que siguen describen preparaciones farmacéuticas que contienen BIBN4096BS o una sal del mismo farmacéuticamente aceptable como sustancia activa:

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Ejemplo 2
Cápsulas para Inhalación de polvo con 1 mg de sustancia activa

Composición:

5	1 cápsula para Inhalación de polvo contiene:	
	sustancia activa	1,0 mg
	lactosa	20,0 mg
	cápsulas de gelatina dura	<u>50,0 mg</u>
		71,0 mg

10 **Método de preparación:**

La sustancia activa se muele hasta el tamaño de partícula que se necesita para Inhalación. La sustancia activa molida se mezcla homogéneamente con la lactosa. La mezcla se carga en cápsulas de gelatina dura.

15 **Ejemplo 3**

Solución Inhalable para respimat® con 1 mg de sustancia activa

Composición:

20	1 pulverización contiene:	
	sustancia activa	1,0 mg
	cloruro de benzalconio	0,002 mg
	edetato disódico	0,0075 mg
	agua purificada hasta	15,0 µl

25 **Método de preparación:**

La sustancia activa y el cloruro de benzalconio se disuelven en agua y se cargan en cartuchos del respimat®.

30 **Ejemplo 4**
Solución Inhalable para nebulizadores con 1 mg de sustancia activa

Composición:

	1 vial contiene:	
35	sustancia activa	0,1 g
	cloruro de sodio	0,18 g

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cloruro de benzalconio	0,002 g
agua purificada hasta	20,0 ml

Método de preparación:

5 La sustancia activa, el cloruro de sodio y el cloruro de benzalconio se disuelven en agua.

Ejemplo 5

Aerosol dosificador accionado por un gas propelente con 1 mg de sustancia activa

10

Composición:

1 pulverización contiene:

sustancia activa	1,0 mg
15 lecitina	0,1 %
gas propelente hasta	50,0 µl

Método de preparación:

20 La sustancia activa micronizada se suspende homogéneamente en la mezcla de lecitina y gas propelente. La suspensión se transfiere a un envase presurizado con una válvula dosificadora.

Ejemplo 6

Spray nasal con 1 mg de sustancia activa

25

Composición:

cada chorro de spray contiene

sustancia activa	1,0 mg
manitol	5,0 mg
30 edetato disódico	0,05 mg
ácido ascórbico	1,0 mg
agua purificada hasta	0,1 ml

Método de preparación:

35 La sustancia activa y los excipientes se disuelven en agua y se transfieren a

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un envase adecuado.

Ejemplo 7

Solución inyectable con 5 mg de sustancia activa por 5 ml

5

Composición:

sustancia activa en forma básica	5 mg
ácido/agente que forma sal en la cantidad necesaria para formar una sal neutra	c.s.
10 glucosa	250 mg
albúmina de suero humano	10 mg
glicofurol	250 mg
agua para inyección hasta	5 ml

15

Preparación:

Se disuelve el glicofurol y la glucosa en agua para inyección (Wfi); se añade albúmina de suero humano; se añade el agente que forma la sal; se disuelve la sustancia activa calentando; se lleva al volumen especificado con Wfi; se transfiere a ampollas bajo atmósfera de gas nitrógeno.

20

Ejemplo 8

Solución inyectable para administración subcutánea que contiene 5 mg de sustancia activa por 1 ml

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Composición:

sustancia activa	5 mg
glucosa	50 mg
polisorbato 80 = Tween 80	2 mg
agua para inyección hasta	1 ml

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Preparación:

Se disuelve la glucosa y el polisorbato en agua para inyección; se disuelve la sustancia activa calentando o utilizando ultrasonidos; se lleva al volumen especificado con Wfi; se transfiere a ampollas bajo atmósfera de gas inerte.

35

Ejemplo 9

Solución Inyectable que contiene 100 mg de sustancia activa por 10 ml

Composición:

5	sustancia activa	100 mg
	dihidrógenofosfato monopotásico	
	= KH_2PO_4	12 mg
	hidrógenofosfato disódico	
	= $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$	2 mg
10	cloruro de sodio	180 mg
	albúmina de suero humano	50 mg
	polisorbato 80	20 mg
	agua para inyección hasta	10 ml

15 **Preparación:**

Se disuelven polisorbato 80, cloruro de sodio, dihidrógenofosfato monopotásico e hidrógenofosfato disódico en agua para inyección (Wfi); se añade albúmina de suero humano; se disuelve la sustancia activa calentando; se lleva al volumen especificado con Wfi; se transfiere a ampollas.

20

Ejemplo 10

Liofilizado que contiene 10 mg de sustancia activa

Composición:

25	sustancia activa en forma básica	10 mg
	ácido/agente que forma sal en la cantidad necesaria	
	para formar una sal neutra	c.s.
	manitol	300 mg
	agua para inyección hasta	2 ml

30

Preparación:

Se disuelve el manitol en agua para inyección (Wfi); se añade el agente que forma la sal; se disuelve la sustancia activa calentando; se lleva al volumen especificado con Wfi; se transfiere a viales; se liofiliza.

35

Disolvente para liofilizar:

polisorbate 80 = Tween 80	20 mg
manitol	200 mg
agua para inyección hasta	10 ml

5

Preparación:

Se disuelven polisorbate 80 y manitol en agua para inyección (Wfi); se transfiere a ampollas.

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Ejemplo 11

Liofilizado que contiene 5 mg de sustancia activa

Composición:

sustancia activa en forma básica	5 mg
disolvente polar o no polar (que se puede separar por liofilización) hasta	1 ml

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Preparación:

20

Se disuelve la sustancia activa en un disolvente adecuado; se transfiere a viales; se liofiliza.

Disolvente para liofilizar:

polisorbate 80 = Tween 80	5 mg
manitol	100 mg
agua para inyección hasta	2 ml

25

Preparación:

30

Se disuelven polisorbate 80 y manitol en agua para inyección (Wfi); se transfiere a ampollas.

Ejemplo 12
Comprimidos que contienen 20 mg de sustancia activa

Composición:		
5	sustancia activa	20 mg
	lactosa	120 mg
	almidón de maíz	40 mg
	estearato de magnesio	2 mg
	Povidona K 25	18 mg
10		

Preparación:

Se mezclan homogéneamente la sustancia activa, lactosa y almidón de maíz; se granulan con una solución acuosa de Povidona; se mezclan con estearato de magnesio; se comprimen en una máquina para formar comprimidos; peso del comprimido 200 mg.

Ejemplo 13
Cápsulas que contienen 20 mg de sustancia activa

Composición:		
20	sustancia activa	20 mg
	almidón de maíz	80 mg
	silíce altamente dispersada	5 mg
	estearato de magnesio	2,5 mg
25		

Preparación:

Se mezclan homogéneamente la sustancia activa, almidón de maíz y silíce; se mezclan con estearato de magnesio; la mezcla se transfiere a cápsulas de gelatina dura del número 3 en una máquina de relleno de cápsulas.

Ejemplo 14
Supositorios que contienen 50 mg de sustancia activa

Composición:		
35	sustancia activa	50 mg

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grasa dura (Adeps solidus) c.s. hasta 1700 mg

Preparación:

5 Se derrite la grasa dura a unos 38°C; se dispersa homogéneamente la sustancia activa molida en la grasa dura derretida; después de enfriar a aproximadamente 35°C se vierte en moldes fríos.

Ejemplo 15

10 **Solución acuosa para administración nasal que contiene 10 mg de sustancia activa**

Composición:

sustancia activa	10,0 mg
ácido clorhídrico en la cantidad necesaria para formar una sal neutra	
15 parahidroxibenzoato (PHB) de metilo	0,01 mg
parahidroxibenzoato (PHB) de propilo	0,005 mg
agua purificada hasta	1,0 ml

Preparación:

20 La sustancia activa se disuelve en agua purificada; se añade ácido clorhídrico hasta que la solución es clara; se añaden PHB de metilo y propilo; la solución se lleva al volumen especificado con agua purificada; la solución se esteriliza por filtración y transfiere a un envase adecuado.

25 **Ejemplo 16**

Solución acuosa para administración nasal que contiene 5 mg de sustancia activa

Composición:

30 sustancia activa	5 mg
1,2-propanodiol	300 mg
hidroxietilcelulosa	5 mg
ácido sórbico	1 mg
agua purificada hasta	1 ml

35

Preparación:

La sustancia activa se disuelve en 1,2-propanodiol; se prepara una solución de hidroxietilcelulosa en agua purificada que contiene ácido sórbico y se añade a la solución de la sustancia activa; la solución se esteriliza por filtración y se transfiere a un envase adecuado.

Ejemplo 17

Solución acuosa para administración intravenosa que contiene 5 mg de sustancia activa

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Composición:

sustancia activa	5 mg
1,2-propanodiol	300 mg
manitol	50 mg
15 agua para inyección (Wfi) hasta	1 ml

Preparación:

La sustancia activa se disuelve en 1,2-propanodiol; la solución se lleva hasta aproximadamente el volumen especificado con Wfi; se añade manitol y se lleva hasta aproximadamente el volumen especificado con Wfi; la solución se esteriliza por filtración, se transfiere a envases individuales y se trata en un autoclave.

Ejemplo 18

Formulación liposómica para inyección intravenosa que contiene 7,5 mg de sustancia activa

25

Composición:

sustancia activa	7,5 mg
lecitina de huevo, p.ej. Lipoid E 80	100,0 mg
30 colesterol	50,0 mg
glicerol	50,0 mg
agua para inyección hasta	1,0 ml

Preparación:

35 La sustancia activa se disuelve en una mezcla de lecitina y colesterol; se

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añade la solución a una mezcla de glicerol y Wfl y se homogeneiza por homogeneización a alta presión o por la técnica del Microfluidizador; la formulación liposómica obtenida se transfiere a un envase adecuado en condiciones asépticas.

5 **Ejemplo 19**

Suspensión para administración nasal que contiene 20 mg de sustancia activa

Composición:

	sustancia activa	20,0 mg
10	carboximetilcelulosa (CMC)	20,0 mg
	tampón de monohidrógenofosfato	
	sódico/dihidrógenofosfato sódico, pH 6,8	c.s.
	cloruro de sodio	8,0 mg
	parahidroxibenzoato de metilo	0,01 mg
15	parahidroxibenzoato de propilo	0,003 mg
	agua purificada hasta	1,0 ml

Preparación:

La sustancia activa se suspende en una solución acuosa de CMC; los demás
20 ingredientes se añaden sucesivamente a la suspensión y la suspensión se lleva al volumen especificado con agua purificada.

Ejemplo 20

Solución acuosa para administración subcutánea con 10 mg de sustancia activa

25

	Composición:	
	sustancia activa	10,0 mg
	tampón de monohidrógenofosfato	
	sódico/dihidrógenofosfato sódico, c.s. hasta pH	7,0
30	cloruro de sodio	4,0 mg
	agua para inyección hasta	0,5 ml

Preparación:

La sustancia activa se disuelve en la solución de tampón fosfato, después de
35 la adición de la sal común, la solución se lleva hasta el volumen especificado con

agua. La solución se esteriliza por filtración, se transfiere a un envase adecuado y trata en un autoclave.

5 **Ejemplo 21**
Suspensión acuosa para administración subcutánea que contiene 5 mg de sustancia activa

Composición:

10	sustancia activa	5,0 mg
	polisorbate 80	0,5 mg
	agua para inyección	0,5 ml

Preparación:

- 15 La sustancia activa se suspende en la solución de polisorbate 80 y se tritura hasta un tamaño de partículas de aproximadamente 1 µm utilizando una técnica de dispersión adecuada (p.ej. molienda húmeda, homogeneización a alta presión, microfluidización, etc.). La suspensión se transfiere a un envase correspondiente en condiciones asépticas.

20

REIVINDICACIONES

- 5 1. Un método de tratamiento o prevención de indicaciones selecciona-
das del grupo formado por cefalea, migraña y cefaleas en racimo, cuyo método com-
prende la co-administración de una cantidad terapéuticamente eficaz de BIBN4096BS
o una sal fisiológicamente aceptable del mismo y una cantidad terapéuticamente eficaz
de otro fármaco antimigrañoso activo (A) a una persona que necesita de dicho trata-
10 miento.
2. El método según la reivindicación 1, caracterizado porque el fárma-
co (A) se selecciona del grupo formado por antieméticos, procinéticos, neurolépticos,
antidepresivos, antagonistas de neuroquinina, anti-convulsionantes, antagonistas del
15 receptor H1 de histamina, antimuscarínicos, β -bloqueantes, α -agonistas y α -
antagonistas, alcaloides del ergot, analgésicos suaves, antiflogísticos no esteroideos,
corticosteroides, antagonistas del calcio y agonistas de 5-HT_{1B/1D}.
3. El método según la reivindicación 2, caracterizado porque el fárma-
20 co (A) se selecciona del grupo formado por alcaloides del ergot y agonistas de
5-HT_{1B/1D}.
4. El método según la reivindicación 3, caracterizado porque porque el
alcaloide del ergot es ergotamina o dihidroergotamina o una de sus sales fisiológica-
25 mente aceptables y el agonista de 5-HT_{1B/1D} es almotriptán, avitriptán, eletriptán, frova-
triptán, naratriptán, rizatriptán, sumatriptán o zolmitriptán o una de sus sales fisiológi-
camente aceptables.
5. El método según la reivindicación 1, caracterizado porque el fárma-
30 co (A) es sumatriptán, zolmitriptán o dihidroergotamina o una de sus sales fisiológica-
mente aceptables.
6. El método de la reivindicación 5, caracterizado porque BIBN4096BS
o una de sus sales fisiológicamente aceptables se administra por vía intravenosa o
35 subcutánea en una dosificación de 0,0001 a 3 mg/kg de peso corporal o por vía oral,

- nasal o inhalativa en una dosificación de 0,1 a 10 mg/kg de peso corporal una, dos o tres veces al día y
- se administra sumatriptán o una de sus sales fisiológicamente aceptables por vía oral en una dosificación de 0,03 a 1,43 mg/kg de peso corporal una, dos o tres veces al día, o
- 5 por vía intravenosa o subcutánea en una dosificación de 0,002 a 0,09 mg/kg de peso corporal una o dos veces al día, o
- por vía rectal en una dosificación de 0,007 a 0,36 mg/kg de peso corporal una o dos veces al día, o
- 10 por vía nasal en una dosificación de 0,006 a 0,29 mg/kg de peso corporal una o dos veces al día, o
- se administra zolmitriptán o una de sus sales fisiológicamente aceptables por vía oral en una dosificación de 0,0007 a 0,036 mg/kg de peso corporal una o dos veces al día, o
- 15 se administra dihidroergotamina o una de sus sales fisiológicamente aceptables por vía oral en una dosificación de 0,001 a 0,07 mg/kg de peso corporal una o dos veces al día.

7. Una composición farmacéutica para tratar o prevenir cefaleas, migraña o cefaleas en racimo, que comprende una cantidad terapéuticamente eficaz de BIBN4096BS o una de sus sales fisiológicamente aceptables y un fármaco antimigrainoso (A) seleccionado del grupo formado por sumatriptán, zolmitriptán y dihidroergotamina o una de sus sales fisiológicamente aceptables como una preparación combinada para administración simultánea o secuencial.

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8. La composición farmacéutica de la reivindicación 7, que comprende una sola unidad de dosificación de 0,1 a 10 mg de BIBN4096BS y una sola unidad de dosificación de 1 a 100 mg de sumatriptán o una sola unidad de dosificación de 0,1 a 2,5 mg de zolmitriptán o

30 una sola unidad de dosificación de 0,1 a 5 mg de dihidroergotamina.

9. Un kit de partes para tratar o prevenir cefalea, migraña o cefaleas en racimo, kit que comprende

(c) un primer envase que contiene una composición farmacéutica que comprende una cantidad terapéuticamente eficaz de BIBN4096BS o una sal

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del mismo fisiológicamente aceptable y uno o más diluyentes y/o vehículos farmacéuticamente aceptables; y

- 5 (d) un segundo envase que contiene una composición farmacéutica que comprende sumatriptán, zolmitriptán o dihidroergotamina o una de sus sales fisiológicamente aceptables y uno o más diluyentes y/o vehículos farmacéuticamente aceptables.

10 10. El kit de partes según la reivindicación 9, kit que comprende sumatriptán o una de sus sales fisiológicamente aceptables en el segundo envase.

15 11. Uso de BIBN4096BS o una de sus sales fisiológicamente aceptables en combinación con otro fármaco antimigrañoso activo (A) para la fabricación de una composición farmacéutica para tratar o prevenir cefalea, migraña o cefaleas en racimo.

20 12. El uso según la reivindicación 11, caracterizado porque el fármaco (A) se selecciona del grupo formado por antieméticos, procinéticos, neurolépticos, antidepresivos, antagonistas de neuroquinina, anti-convulsionantes, antagonistas del receptor H1 de histamina, antimuscarínicos, β -bloqueantes, α -agonistas y α -antagonistas, alcaloides del ergot, analgésicos suaves, antiflogísticos no esteroideos, corticosteroides, antagonistas del calcio y agonistas de 5-HT_{1B/1D}.

25 13. El uso según la reivindicación 12, caracterizado porque el fármaco (A) se selecciona del el grupo formado por agonistas de 5-HT_{1B/1D} y alcaloides del ergot.

30 14. El uso según la reivindicación 13, caracterizado porque el alcaloide del ergot es ergotamina o dihidroergotamina o una de sus sales fisiológicamente aceptables y el agonista de 5-HT_{1B/1D} es almotriptán, avavriptán, eletriptán, frovatriptán, naratriptán, rizatriptán, sumatriptán o zolmitriptán o una de sus sales fisiológicamente aceptables.

35 15. El uso según la reivindicación 14, caracterizado porque el fármaco (A) es sumatriptán, zolmitriptán o dihidroergotamina o una de sus sales fisiológicamente aceptables.

16. El uso de BIBN4096BS o una de sus sales fisiológicamente aceptables para la fabricación de una composición farmacéutica o un kit de partes según cualquiera de las reivindicaciones 7 a 10.

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RESUMEN

- 5 La presente Invención se refiere a un método de tratamiento o prevención de cefalea, migraña o cefaleas en racimo, método que comprende la co-administración de una cantidad terapéuticamente eficaz del compuesto
- A = 1-[N²-[3,5-Dibromo-N-[[4-(3,4-dihidro-2(1H)-oxoquinazolin-3-il)-1-piperidinil]-carbonil]-D-tirosil]-L-Ilsil]-4-(4-piridinil)-piperazina [BIBN4096BS]
- 10 o una de sus sales fisiológicamente aceptables y una cantidad terapéuticamente eficaz de un segundo fármaco antimigrañoso activo, particularmente sumatriptán, zolmitriptán o dihidroergotamina o una de sus sales fisiológicamente aceptables, así como a las correspondientes composiciones farmacéuticas y su preparación.

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SUPERINDUSTRIA Y COMERCIO
Radicacion : 04012009 00000000 Folios: 09
Fecha (IMP): 2004-02-12 17:37:39
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES
NIT : 80017608.

RECIBO OFICIAL DE CAJA : 04 - 8,090
FECHA : FEBRERO 2 DE 2004

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	DANCO POPULAR	050-00110-6	10497415	02/02/2004	66,752,000.00

***** CONCEPTO *****

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	422,000.00
	TOTAL :	422,000.00

SON: CUATROCIENTOS VEINTIDOS MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Colo 13736 841-0247

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL
TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION	()	()
MODELO DE UTILIDAD	()	()
- Indicación de que se solicita la concesión de una patente.	()	()
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	()	()
- Descripción de la invención.	()	()
- Dibujos de ser estos pertinentes.	()	()
- Comprobante de Pago de las tasas establecidas.	()	()

COMPLETA () INCOMPLETA ()

DISEÑO INDUSTRIAL ()

- Indicación de que se solicita el registro de Diseño Industrial	()	()
- Datos de identificación del solicitante o de la persona que presenta la solicitud.	()	()
- Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	()	()
- Comprobante de pago de las tasas establecidas	()	()

COMPLETA () INCOMPLETA ()

ESQUEMA DE TRAZADO ()

- Indicación de que solicita el registro de un Esquema de trazado.	()	()
- Datos de identificación del solicitante o de la persona que presenta La solicitud.	()	()
- Representación gráfica del esquema de trazado	()	()
- Comprobante de pago de las tasas establecidas.	()	()

COMPLETA () INCOMPLETA ()

Firma Responsable.

Fecha:



2020
Bogotá, D.C.,

Doctor:
Emilio Ferrero
Apoderado
Boshringer Ingelheim Pharma GmbH & CO. KG

Oficio N°
65188

ASUNTO:	Radicación N°	04 012008
	Solicitud Internacional	PCT/EP02/08993
	Fecha inicio fase nacional	17/03/2004
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

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

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

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

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


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

El anterior requerimiento fue notificado por fijación en lista de fecha 21 Mayo 2004.