



No. 08-124345-00003-0000

Fecha: 2010-02-25 17:05:05 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eje: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 56

FORMULARIO ÚNICO DE OPOSICIÓN

①

OPOSICIÓN A:

- | | |
|---|---|
| ☒ Patente de Invención | ☐ Marca Colectiva |
| ☐ Patente de Modelo de Utilidad | ☐ Marca de Certificación |
| ☐ Diseño Industrial | ☐ Lema Comercial |
| ☐ Esquema de Trazado para Circuitos Integrados | |
| ☐ Marcas de Productos o Servicios | |

②

Número del expediente: **08 124345**

Solicitante: **NOVARTIS AG**

**SOLICITUD
PUBLICADA**

Apoderado: **ALVARO CORREA ORDÓÑEZ**

Título de la nueva creación o denominación del signo:

COMPOSICIONES FARMACEUTICAS DE ANTICUERPO ANTAGONISTA ANTI-CD40

Gaceta: **610**

③ **OPOSICIÓN PRESENTADA POR:**

SOLICITANTE	Nombre: GYNOPHARM	IDENTIFICACIÓN	
	Dirección: Carrera 14 N° 94-44 piso 7 torre b Nacionalidad o Domicilio: COLOMBIA Lugar de Constitución: BARRANQUILLA	C.C. ☐ NIT ☒ C.E. ☐ Otro ☐ Cual _____	
	Teléfono: 2 36 84 95 Fax: _____ E-mail: _____	Número 802,006,279-4	
REPRESENTANTE O APODERADO	Nombre: CIELO ANGELA PEÑA RODRIGUEZ	IDENTIFICACIÓN	
	Dirección: CARRERA 13 N°. 119-95 Teléfono: (571)213 12 13 Fax: (571)612 19 79 E-mail: negocios@optimum-co.com	C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual _____	
		Número 51.940.252 TP 82701	

④ **FUNDAMENTOS DE LA OPOSICIÓN:**

Art. 14, 16, 18, 20 y 30 de la Decisión 486 de la CAN

Causal: **No cumple con los requisitos de patentabilidad.**

Signo opositor: _____

Justificación: _____

La presente solicitud no cumple con los requisitos de patentabilidad dado que lo revelado, ya se encontraba en el estado de la técnica o es posible derivarlo de la misma tal y como se demostrará en el capítulo "Fundamento de Hechos".

⑤ Comprobante de pago No. _____

Fecha _____

⑥ ANEXOS

- ☒ Comprobante de pago de la tasa.
- ☒ Poderes, si fuere el caso.
- ☒ Pruebas de los fundamentos de la oposición.
- ☐ Documentos que acrediten el legítimo interés, si fuere el caso.
- ☒ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.

⑦

NOMBRE: CIELO ANGELA PEÑA RODRIGUEZFIRMA: 

C.C. 51.940.252

TP. 82701

Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia : Expediente N° 08 124345

Asunto : Oposición a la solicitud de patente de Invención titulada
"COMPOSICIONES FARMACEUTICAS DE
ANTICUERPO ANTAGONISTA ANTI-CD40"

Solicitante : NOVARTIS AG Y XOMA TECHNOLOGY LTD

Opositora : GYNOPHARM S.A.

Publicada en la Gaceta de la Propiedad Industrial

N° 610 del 30 de noviembre de 2009

Yo, **CIELO ANGELA PEÑA RODRIGUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 08 124345 del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad **GYNOPHARM S.A.** conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la Patente de Invención titulada "COMPOSICIONES FARMACEUTICAS DE ANTICUERPO ANTAGONISTA ANTI-CD40", cuyos titulares son **NOVARTIS AG y XOMA TECHNOLOGY LTD, A.G.**, y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

1. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en particular ANTICUERPOS ANTI-CD40. Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

2. FUNDAMENTOS DE HECHOS

2.1. La solicitud objeto de la presente fue presentada el 21 de noviembre de 2008 reivindicando prioridad bajo la solicitud US20060794011P del 2006-04-21; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 610 del 30 de Noviembre de 2009, cuya publicación internacional corresponde a la WO2007124299 del 2007-11-01.

2.2. La solicitud colombiana 08 124345 objeto de la presente oposición, se refiere a una composición farmacéutica líquida estable que comprende: a) Un anticuerpo monoclonal anti-CD40 antagonista como un componente terapéuticamente o profilácticamente activo, en donde dicho anticuerpo monoclonal es capaz de unirse específicamente a un antígeno CD40 de humano expresado sobre la superficie de una célula B humana, dicho anticuerpo monoclonal está libre de actividad agonista

significativa que se une al antígeno CD40 expresado sobre la superficie de dicha célula B; b) una cantidad de arginina en su forma ácida (arginina-HCl) suficiente para hacer que dicha composición sea casi isotónica; y c) un agente de amortiguación para mantener el pH de dicha composición dentro de un rango de aproximadamente pH 5.0 a aproximadamente pH 7.0, en donde dicho agente de amortiguación es un amortiguador de citrato/ácido cítrico.

2.3. En primera instancia, se debe advertir que en las reivindicaciones 35 a la 44 además de la 59 y la 60 la solicitud objeto de la presente oposición se refiere a un método terapéutico y no sólo a la composición farmacológica o a un método de fabricación mediante la cual se obtenga un producto tangible y según la legislación, decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento (...)"*, los usos no están contemplados como patentables; y, Artículo 20.- *"No serán patentables (...) d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales"*. Solo serán patentables los productos o procedimientos. Por lo tanto a luz de la norma, dicha materia referente al método no sería patentable.

2.4. Con base en el artículo 14 de la Decisión 486 de la CAN que consagra: *"Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*, tenemos que las invenciones objeto de patente deben ser nuevas y tener nivel inventivo. Bien, pues antes de la fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afectan la patentabilidad de la presente solicitud:



- D1: WO 99/37329 publicada el 29 de julio de 1999.
- D2: US 2005/175611 publicada el 11 de agosto de 2005.

2.5. Ahora bien, el documento D1, particularmente en la descripción revela una formulación farmacéutica que comprende un anticuerpo humanizado, un buffer de citrato (5 mm a 20 mm) y el pH de la formulación es 5.3 a 7.2. Preferentemente, el documento D1 revela que el pH es 5.5, el buffer de citrato está presente en 10 mm (p. 3 l. 4-11, p. 5 l. 1-3), donde NaCl es agregado para hacer la solución isotónica (p. 6 l. 10-11). Igualmente, en la anterioridad D1 se define claramente que las formulaciones eran estables en 5° C durante 24 meses (p. 9 l. 7-10). Por su parte, el documento D2 describe una preparación farmacéutica que comprende un anticuerpo anti-EGFR (0.1-50 mg/ml) (párrafo [22]), buffer de citrato (10 mm) (párrafo [23]), el pH 5.5 (el párrafo [24]), arginina-HCl (100 mm) (párrafo [26] - [27]), Tween (0.001- 1.0 %) (párrafo [28] - [30]). Según este documento D2, la preparación es estable por un periodo de hasta 2 años en temperaturas elevadas, p. ej. 25°C (párrafo [25]). De similar forma, se ilustra en esta anterioridad D2 que la osmolalidad es de 250-350 mOsmol/kg (párrafo 31) y se advierte que el NaCl es usado como modificador isotónico (párrafo [32]). Esta anterioridad D2 también revela que contiene además antioxidantes (párrafo [33]) y define en particular que la preparación acuosa comprende un anticuerpo en una cantidad de 5 mg/ml, 10 mm de buffer de citrato, un pH de 5.5, 100 mm de arginina, 100 mm NaCl y el 0.01 % de Tween 80 (polioxietileno (20) sorbitan monooleate) (párrafo [34]). Por lo tanto, es posible deducir que para un experto en la materia con la combinación de la información del documento D1 con el documento D2 de similar propósito, apoyado por el hecho de utilizar un anticuerpo anti-CD40 sólo en casos de formulaciones particulares (ya que al parecer el buffer, el PH y los excipientes son dependientes de la secuencia o estructura del anticuerpo utilizado en la

formulación) cualquier persona versada en la materia puede llegar de manera evidente y obvia a la presente solicitud objeto de oposición para obtener una composición farmacéutica líquida estable que comprende un anticuerpo monoclonal anti-CD40 antagonista; una cantidad de arginina; y un agente de amortiguación para mantener el pH. Así entonces la presente solicitud a la luz de los documentos D1 y D2 en combinación, carece de altura inventiva.

2.6. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 08 124345 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con dos de los tres requisitos necesarios para su protección.

2.7. Que por consiguiente, respecto a la solicitud pretendida se tiene que:

2.7.1. **CARENCIA DE ALTURA INVENTIVA.** Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- *"Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica."* A la fecha de prioridad, 21 de abril de 2006, a partir del documento D2 en combinación con D1, puede llegar de manera evidente a una composición farmacéutica líquida estable que comprende un anticuerpo monoclonal anti-CD40 antagonista; una cantidad de arginina; y un agente de amortiguación para mantener el pH, para la prevención y tratamiento de cáncer, o dolencias relacionadas con el anticuerpo de la formulación, según lo revelado en el capítulo reivindicatorio.

2.7.2. **CARENCIA DE APLICACIÓN INDUSTRIAL** La Decisión 486 de la CAN consagra en su artículo 14 lo siguiente: *"Los países miembros otorgarán patentes*

para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial". La presente solicitud carece de aplicación Industrial ya que como se demostró anteriormente, en los apartados 35 a 44, 59 y 60 del capítulo reivindicatorio se reclama un método terapéutico y este no es aplicable industrialmente porque primero no se obtiene un producto o proceso; y segundo no es reproducible o repetible a escala industrial. Por lo tanto, el objeto de la presente invención referido a los usos, no cumple con el requisito de la aplicación industrial.

2.8. Dado lo anterior, es posible deducir que la solicitud y lo reivindicado no es objeto de patentabilidad pues es contrario a lo que dicta la Decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- "Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial". La solicitud pretendida no cumple con dos de los tres requisitos de patentabilidad.

2.9. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y en consecuencia negar el registro a la solicitud de patente titulada "COMPOSICIONES FARMACEUTICAS DE ANTICUERPO ANTAGONISTA ANTI-CD40", cuyos titulares son NOVARTIS AG Y XOMA TECHNOLOGY LTD, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 610 del 30 de noviembre de 2009.

3. PRUEBAS

De conformidad con lo dispuesto por las normas vigentes, solicito a usted tener como prueba en este asunto los siguientes:

- D1: WO 99/37329 publicada el 29 de julio de 1999.
- D2: US 2005/175611 publicada el 11 de agosto de 2005.

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

- 4.1. Numeral 1 del artículo 586 del Código de Comercio.
- 4.2. Artículo 42 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.
- 4.3. En las demás normas concordantes.

5. ANEXOS

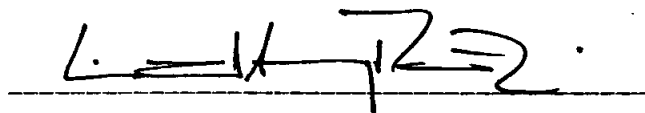
Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

1. Poder para actuar en el presente.
 2. Documento que acredita al representante legal de GYNOPHARM S.A.
 3. Recibo de caja del respectivo pago de tasa.
 4. Copias de los documentos:
- D1: WO 99/37329 publicada el 29 de julio de 1999.
 - D2: US 2005/175611 publicada el 11 de agosto de 2005.

6. NOTIFICACIONES

Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas situadas en la Carrera 13 N° 119-95, Of. 104 de esta ciudad de Bogotá.

Señor Superintendente,

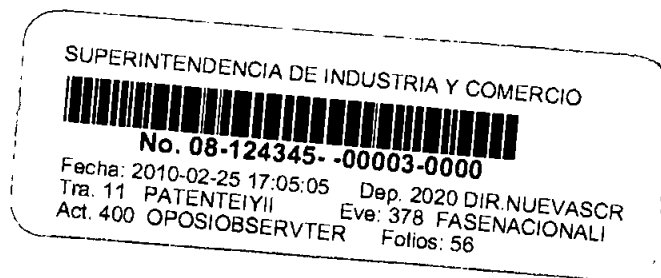


CIELO ANGELA PEÑA RODRIGUEZ
C.C. 51'940.252 de Bogotá
T.P.A. 82701 del C.S. de la J.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 15,535
FECHA : FEBRERO 25 DE 2010



***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
GYNOPHARM S.A.	CONSIGNACION	BANCO DE BOGOTA	062754387	45812406	29/01/2010	295,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04	PRESENTACION DE OBSERVACIONES	
		12 MARCAS Y LEMAS COMERCIALES	295,000.00
		TOTAL :	\$ 295,000.00

SON: DOSCIENTOS NOVENTA Y CINCO MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

PODER ESPECIAL

Yo, **LUIS PALACIOS ARAGÓN**, mayor de edad y vecino de la ciudad de Barranquilla (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Representante Legal de la sociedad **GYNOPHARM S.A.** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorgo a la doctora **CIELO ANGELA PEÑA RODRIGUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 82701 del C.S. de la J., poder especial, amplio y suficiente, para presentar ante ese Despacho una remisión de información a la solicitud de patente No. 08 124345, titulada "COMPOSICIONES FARMACEUTICAS DE ANTICUERPO ANTAGONISTA ANTI-CD40", cuyo titular es **NOVARTIS AG Y XOMA TECHNOLOGY LTD**, publicada en la gaceta No. 610 del 30 de noviembre de 2009.

Nuestro apoderado queda facultado, de manera expresa, para realizar todo tipo de actos necesarios para llevar a cabo el trámite de dicha remisión, incluyendo, sin limitación, preparar y presentar solicitudes, hacer declaraciones, pagar tasas, contribuciones e impuestos, recabar los títulos o certificados. Asimismo quedan autorizados para impugnar administrativa todo lo que fuere resuelto en el expediente a que se hace expresa referencia en el presente poder, con todas las facultades generales y específicas que fuera requerido para ella.

De la misma manera, además de las facultades que le confiere la naturaleza del presente mandato, se encuentran facultados para recibir, desistir, transigir, sustituir, y reasumir el presente poder, incoar acciones, interponer recursos y demás facultades conferidas por la ley.

Dado y Firmado en _____ (Colombia) a los ____ días del mes de ____ de 2010.

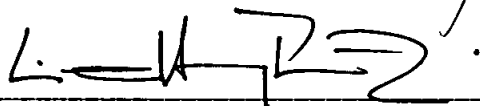
GYNOPHARM S.A.

Cédula de Extranjería: No. 319788.

NIT: 802.006.2794

Representante Legal

Acepto:



CIELO ANGELA PEÑA RODRIGUEZ

C.C. 51'940.252 de Bogotá

T.P.A. 82701 del C.S. de la J.





NOTARIA DIECIOCHO DEL
CÍRCULO DE BOGOTÁ D.C. 18
LA HUELLA SE AUTENTICA POR
SOLICITUD DEL INTERESADO.

DILIGENCIA DE PRESENTACIÓN

El Notario Dieciocho del Circuito de Bogotá,

D.C., hace constar que el presente documento

fue presentado personalmente por:

PALACIOS ALACON

quien exhibió la C.E. 3191788

de 189 y Tarjeta Profesional

No 189 C.S.J., y declaró que

la firma y la huella que aparecen en el
presente documento son suyas.

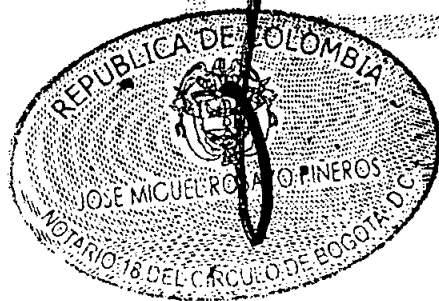
BOGOTÁ, D.C. 17 FEB 2010

FIRMA

EL NOTARIO



HUELLA DEL
INDICE DERECHO



01

* 8 8 4 0 5 0 2 6 *

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2010/01/07

HORA: 09:27:26

OPERACION: 03ERP0107026

PAGINA: 1

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE BARRANQUILLA, CON FUNDAMENTO EN LAS INSCRIPCIONES DEL REGISTRO MERCANTIL:

C E R T I F I C A

Que por Escritura Pública No. 3,551 del 17 de Dic/bre de 1997, otorgada en la Notaria 3a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 18 de Dic/bre de 1997 bajo el No. 72,965 del libro respectivo; fue constituida la sociedad-----
anonima denominada GYNOPHARM S.A., -----

C E R T I F I C A

Que dicha sociedad ha sido reformada por las siguientes escrituras y/o documentos privados:

Numero	aaaa/mm/dd	Notaria	No. Insc o Reg	aaaa/mm/dd
532	1999/03/25	Notaria 3a. de Barranquilla	80,373	1999/04/13

C E R T I F I C A

Que de acuerdo con la(s) escritura(s) arriba citada(s), la sociedad se rige por las siguientes disposiciones:

DENOMINACION O RAZON SOCIAL:

GYNOPHARM S.A.-----

DOMICILIO PRINCIPAL: Barranquilla.

NIT No: 802.006.279-4.

MATRICULA MERCANTIL: 245,470.

C E R T I F I C A

Dirección para notificaciones judiciales:

CR 49 C No 80 - 125 OF 512.

De la ciudad de Barranquilla.

C E R T I F I C A

DURACION: El término de duración de la sociedad se fijó hasta el 16 de Dic/bre de 2047.

C E R T I F I C A

OBJETO SOCIAL: a) La fabricacion de capsulas y otro productos similares a partir de materiales tales como gelatinas u otros de distinta naturaleza, que puedan ser utilizados como envases o recipientes de productos y sustancias quimicas, farmaceuticas y cosmeticas, para

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2010/01/07

HORA: 09:27:26

OPERACION: 03ERP0107026

PAGINA: 2

uso y consumo humano y veterinario. b) La investigacion, desarrollo y fabricacion de toda clase de productos y sustancias quimicas, farmaceuticas y cosmeticas para uso y consumo humano, animal y vegetal. c) La compra y venta de materias primas, insumos y productos intermedios necesarios para los procesos de fabricacion de sustancias quimicas, farmaceuticas y cosmeticas, asi como la comercializacion interna y externa de los productos terminados. d) La compra, venta, importacion, exportacion y distribucion de toda clase de elementos instrumentales y equipos, medicos, quirurgicos, odontologicos y hospitalarios para la salud humana y animal. e) Actuar como representante o agente de personas naturales y juridicas nacionales y extranjeras en la realizacion de operaciones o transacciones relacionadas con la industria farmaceutica y en especial con cualesquiera de las actividades descritas en los literales a), b), c) y d) antes transcritos. f) Prestar los servicios de asesoria y consultoria en las areas administrativa, de mercadeo, analisis clinico, asistencia tecnica, investigacion, costos y produccion exportaciones, importaciones, ventas, relacionadas con iguales o similares actividades a las que constituyen el objeto de GYNOPHARM S.A., asi como los de publicidad y promocion de productos quimicos, cosmeticos y farmaceuticos para uso humano, animal o industrial. g) Adquirir, operar, administrar y explotar, a cualquier titulo, empresas o establecimientos dedicados a la investigacion, desarrollo, fabricacion o comercializacion de productos quimicos, farmaceuticos, hospitalarios o cosmeticos. En desarrollo de su objeto principal, la sociedad podra tomar interes social como accionista, socio o fundador de empresas que tengan igual o similar objeto; comprar, vender, importar y exportar maquinarias, insumos y repuestos requeridos para el desarrollo de sus actividades; tomar dinero en prestamo, financiar y garantizar las operaciones comerciales que celebre con terceros relativas a su objeto; celebrar y ejecutar todo tipo de actos y contratos necesarios para desarrollar sus operaciones; girar, aceptar, otorgar y protestar todo tipo de titulos valores e instrumentos negociables; comprar, vender y constituir gravámenes sobre bienes muebles e inmuebles; designar representantes o apoderados en el pais y en el exterior y, en

*** CONTINUA ***



CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2010/01/07

HORA: 09:27:26

OPERACION: 03ERP0107026

PAGINA: 3

general, realizar cualquier acto o negocio que sea necesario o con-
veniente para el desarrollo de su objeto social y para la mejor pro-
teccion de sus intereses corporativos o lo de sus socios.-----

C E R T I F I C A

CAPITAL

Nro Acciones

Valor Acción

Autorizado:

\$*****4,000,000,000 *****4,000,000 *****1,000

Suscrito

\$*****2,672,646,000 *****2,672,646 *****1,000

Pagado

\$*****2,672,646,000 *****2,672,646 *****1,000

C E R T I F I C A

ADMINISTRACION: Seran funciones de la junta directiva, entre otras: Autorizar cualquier acto o contrato cuya cuantia sea superior al equivalente en pesos Colombianos a cincuenta mil dolares de los Estados Unidos de America (US\$50.000.00), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion y para enajenar o gravar bienes inmuebles y demas activos fijos de la sociedad, cualquiera que sea la cuantia de la transaccion. Las demas que le sean propias y no esten atribuidas a otro organo social y las que le correspondan en virtud de la ley. la sociedad tendra un Gerente General, quien ejercera la administracion y representacion legal de la sociedad y tendra las siguientes atribuciones, entre otras: Ejercer la representacion legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos Colombianos a cincuenta mil dolares de los Estados Unidos de America (US\$50.000.00), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto. Para enajenar, a cualquier titulo, bienes inmuebles de la sociedad o constituir gravámenes sobre los mismos, debera obtener la aprobacion de la junta directiva, cualquiera que sea la cuantia de la transaccion; o las demas funciones que le corres-

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CAMARA DE COMERCIO DE BARRANQUILLA

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pondan. como representante legal por disposicion de la ley, de estos estatutos o de la junta directiva. El Gerente General tendra un suplente, designado por la junta directiva, quien lo reemplazara con identicas facultades en sus faltas temporales, absolutas o meramente accidentales, sin que sea necesario para ello acreditar la ausencia del principal.-----

C E R T I F I C A

Que según Acta No. 15 del 18 de Febrero de 2008 correspondiente a la Asamblea de Accionistas en Bogota, de la sociedad:

GYNOPHARM S.A.-----
cuya parte pertinente se inscribió en esta Cámara de Comercio, el 25 de Febrero de 2008 bajo el No. 137,919 del libro respectivo, fueron hechos los siguientes nombramientos:

CLASE: JUNTA DIRECTIVA

Principales

- | | |
|---|--------------------|
| 1. Llobet Poal Manuel | CC.*****14,670,196 |
| 2. Zanatta Reheman Leonardo Andres | CC.*****2,760,271 |
| 3. Munoz Marroquin Diego | CC.*****7,688,292 |
| 4. Montealegre Gonzalez Andres Leonardo | CC.*****79,950,262 |

Suplentes

- | | |
|-----------------------------------|--------------------|
| 1. Agudelo Pelaez Luis Hernando | CC.*****14,238,997 |
| 2. Aroca Almanza Arleth Ayelina | CC.*****36,718,415 |
| 3. Penaranda Urbina Adriana Paola | CC.*****53,120,683 |
| 4. tovar Vasquez Ruth | CC.*****52,175,756 |

C E R T I F I C A

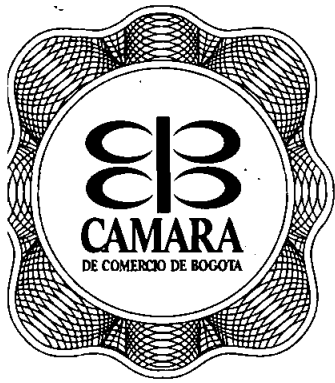
Que según Acta No. 18 del 30 de Octubre de 2003 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: GYNOPHARM S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 06 de Nov/bre de 2003 bajo el No. 107,783 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Gerente General.	
Palacios Aragon Luis Alberto	CE.*****319,788

C E R T I F I C A

Que según Acta No. 49 del 03 de Marzo de 2008 correspondiente a la

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Junta Directiva en Barranquilla, de la sociedad: GYNOPHARM S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 11 de Marzo de 2008 bajo el No. 138,342 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre

Identificación .

Suplente del.. Gerente.

Mollajoli Centurion Andres Fernando

CE.*****351,283

C E R T I F I C A

Que según Acta No. 19 del 30 de Abril de 2009 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: GYNOPHARM S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 27 de Mayo de 2009 bajo el No. 149,314 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre

Identificación

Revisor Fiscal.

PENALOSA · AUDITORES & ASOCIADOS S.A.

Nil.*****830,095,635

C E R T I F I C A

Que por Documento Privado del 11 de Mayo de 2009, otorgado en Bogota por Peñalosa Auditores & Asociados S.A. inscrito en esta Cámara de Comercio, el 27 de Mayo de 2009 bajo el Nro 149,315 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre

Identificación

Designado: Revisor Fiscal Ppal

Padilla Romero Ivan Dario

CC. *****80,025,798

Designado: Revisor Fiscal Suplente

Gomez Preciado Clara Judith

CC.*****52,544,226

C E R T I F I C A

Que segun Documento Privado de fecha 10 de Octubre del 2.000, inscrito en esta Camara de Comercio el 23 de Noviembre del 2.000 bajo el Nò. 1.872 del libro repectivo, consta que el senor RUBEN MINSKI GONTOVNIK C.C. No. 7.463.982, actuando como Presidente y representante legal de la sociedad GYNOPHARM S.A., otorga Poder Especial, Amplio y Suficiente a KAREN JENNIFER FIGUEROA GARCIA C.C. No. 32.-732.070, para que en nombre y representacion de la sociedad suscriba todas las declaraciones cambiarias a que esta obligada GYNOPHARM

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

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S.A., en el giro normal de sus negocios y operaciones sociales.-----

C E R T I F I C A

Que segun Documento Privado de fecha 10 de Octubre del 2.000, inscrito en esta Camara de Comercio el 12 de junio del 2.002, bajo el 2.164 del libro respectivo, consta que el señor JORGE CASTELLANOS MARTINEZ, identificado con C.C.No.19.460.039, actuando como representante legal de la sociedad GYNOPHARM S.A, otorga Poder Especial Amplio y Suficiente a KAREN FIGUEROA GARCIA, identificada con la cedula de ciudadanía No.32.732.070 de Barranquilla, mediante documento privado de octubre 10/2000, inscrito en la Camara de Comercio de Barranquilla bajo el No.1.872 del libro respectivo, para que en representacion de GYNOPHARM S.A, suscriba las declaraciones cambiarias a los que esta obligada GYNOPHARM S.A. en el giro ordinario de sus negocios y operaciones sociales.-----

C E R T I F I C A

Que por Escritura Pública No. 2,404 del 28 de Mayo de 2009, otorgada en la Notaria la. de Bogota cuya parte pertinente se inscribió en esta Cámara de Comercio, el 02 de Julio de 2009 bajo el No. 3,948 del libro respectivo,-----
consta que el señor LUIS ALBERTO PALACIOS ARAGON con CE No.319788, en su calidad de Representante Legal de GYNOPHARM S.A., manifesto que confiere poder general, amplio y suficiente a la Doctora -----
CAROLINA MARIA ROMERO CERON, identificada con cedula de ciudadanía numero 52.352.190, para que en nombre de la sociedad GYNOPHARM -----
S.A., promueva y defienda los intereses de la sociedad judicial y extrajudicialmente, en toda especie de gestiones y actuaciones ante las autooridades administrativas o jurisdiccionales en especial ----
para: a) Recibir notificaciones de cualesquiera tipo de actos -----
emanados de las autoridades administrativas o judiciales. b) -----
Presentar recursos por la via administrativa o judicial, renunciar a terminos, desistir, conciliar, transigir y modificar. c) Elevar peticiones y solicitar informacion a las autoridades -----
administrativas y jurisdiccionales. d) Presentar demandas ante las autoridades administrativas y judiciales.-----

C E R T I F I C A

*** CONTINUA ***



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Que en esta Cámara de Comercio no aparecen inscripciones posteriores de documentos referentes a reforma, disolución, liquidación o nombramientos de representantes legales de la expresada sociedad.

C E R T I F I C A

Que su última Renovación fue el: 31 de Marzo de 2009.

La información sobre embargos de establecimiento se suministra en Certificados de Matrícula, la de contratos sujetos a registro, en Certificados Especiales.

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Que los actos de registro aquí certificados quedan en firme cinco días hábiles después de la correspondiente inscripción, siempre que, dentro de dicho término, no sean objeto de los recursos de reposición ante esta entidad, y/o de apelación para ante la Superintendencia de Industria y Comercio.



PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 39/395	A1	(11) International Publication Number: WO 99/37329 (43) International Publication Date: 29 July 1999 (29.07.99)
(21) International Application Number: PCT/SE99/00049 (22) International Filing Date: 15 January 1999 (15.01.99) (30) Priority Data: 9800170-4 22 January 1998 (22.01.98) SE 9800766-9 9 March 1998 (09.03.98) SE (71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): FLINK, Ola [SE/SE]; Astra Arcus AB, S-151 85 Södertälje (SE). PETRÉN, Sven [SE/SE]; Astra Arcus AB, S-151 85 Södertälje (SE). (74) Agent: ASTRA AKTIEBOLAG; Intellectual Property, Patents, S-151 85 Södertälje (SE).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, 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, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: PHARMACEUTICAL FORMULATION COMPRISING AN ANTIBODY AND A CITRATE BUFFER (57) Abstract The present invention relates to an isotonic pharmaceutical formulation comprising an antibody and a buffer, wherein the antibody is present at 0.5 mg/ml to 10 mg/ml, the buffer is a citrate buffer present at 5 mmol/l to 20 mmol/l and the pH of the formulation is 5.3 to 7.2. The invention also relates to a method for the storage of antibodies by use of such formulations and to the use of such formulations in therapy.		

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PHARMACEUTICAL FORMULATION COMPRISING AN ANTIBODY AND A CITRATE BUFFER

The invention relates generally to antibody formulations and particularly to stabilised
5 antibody formulations for storage and for therapeutic administration.

Purified proteins, particularly those produced using recombinant DNA technology are now
well established as pharmaceutical agents. Such proteins do however present a range of
problems associated with their stable formulation. Many protein preparations are
10 particularly unstable in dilute solutions and must be formulated in such a way as to prevent
significant levels of denaturation, agglomeration or degradation. These problems are
particularly acute in the formulation of large proteins such as immunoglobulins.

Immunoglobulins or antibodies are known to be prone to form aggregates and particulates
in solution and this has long provided special problems in generating suitable formulations
15 for the storage and administration of therapeutic antibodies. Existing antibody formulations
frequently require to be filtered before injection to remove aggregates or particulate matter
which is inconvenient and tends to reduce the accuracy of the injected dose.

Various attempts have been made to overcome the problems of antibody formulation:

20 EP 0 073 371 describes intravenously administrable immunoglobulin compositions which
have their pH adjusted to 3.5 to 5.0 as proteins are known to be more stable at low pH.
Such low pHs however tend to result in undesirable reactions at the site of injection .

25 US 4650772 describes a method for stabilising thermally unstable monoclonal antibodies
which requires the presence of 0.25% to 5% hydrolysed ovalbumin. The use of ovalbumin
in pharmaceutical formulations results in the induction of an allergic response which
prevents its effective use for repeated administrations.

30 WO 90/11091 describes the use of maltose and buffers in a lyophilised formulation of
monoclonal antibodies. Lyophilisation is however an expensive process and the need to

resuspend the formulation prior to administration adds to the complexity of the treatment regimen. It was suggested that citrate buffer may be used to buffer the pH at between 3.0 and 6.0.

5 The present invention provides a more simple antibody formulation than those presently known, providing a formulation which is both suitable for administration and has improved storage properties. Existing antibody formulations require the use both of a stabiliser and of a buffer. However antibodies in formulations of the present invention are stabilised only by citrate buffer in a saline solution at a physiologically preferable pH.

10

There is therefore provided according to the present invention, an isotonic pharmaceutical formulation comprising an antibody and a buffer, wherein the antibody is present at 0.5mg/ml to 10mg/ml, the buffer is a citrate buffer present at 5mmol/l to 20mmol/l and the pH of the formulation is 5.3 to 7.2.

15

A citrate buffer for use in the present invention may be generated by dissolution of free citric acid or preferably a pharmaceutically acceptable salt of citrate, preferably a sodium salt.

20

A formulation of the present invention may be generated by solubilising the relevant antibody, preferably in saline and adding an amount of citrate buffer necessary to obtain a pH of the solution in the range 5.3 to 7.2. The citrate buffer is preferably present at 5mmol/l to 20mmol/l.

25

A formulation of the present invention may additionally contain other substances desirable for therapeutic efficacy of the antibody e.g. chelators, or other therapeutic compounds desirable to be coformulated with the antibody but it is preferably substantially free of any additional compound known for use in antibody stabilising e.g. Tween, mannitol or maltose. By 'substantially free' it is meant that such additional compounds known for use in
30 antibody stabilising formulations may not be present in formulations of the present

invention in an amount capable alone or in combination with one or more other stabilisers, of having a stabilising effect upon an antibody in a formulation.

In preferred embodiments of the present invention citrate buffer is present in the
5 formulation at 7.5mmol/l to 15mmol/l and most preferably at 10mmol/l. Any
pharmaceutically acceptable citrate buffer may be used in the present invention but the
citrate buffer is preferably sodium citrate. It is more preferable that sodium citrate
dihydrate is used and most preferable that the citrate buffer be generated from a mixture of
sodium citrate dihydrate and citric acid monohydrate. In the preferred embodiments of the
10 present invention, the formulation contains about 2.4 mg/ml sodium citrate dihydrate and
about 0.387 mg/ml citric acid monohydrate.

The present invention is suitable for the formulation of any antibody or antibody fragment.
Any reference to an antibody herein will be taken to include a fragment of such antibody.
15 The antibody for use in a formulation of the present invention may be natural or
recombinant and may be generated according to any known technique. Natural antibodies
may be those isolated either by purification from body fluids or from cell lines and may be
polyclonal or monoclonal antibodies. Particularly preferred antibodies for use in
formulations of the present invention are recombinant antibodies produced from
20 engineered cell lines. Such cell lines will have been engineered to express the relevant
antibody gene. The antibody gene may either be a human gene or a gene from another
species which has been humanised by modification of the native sequence to prevent
rejection when administered to a human, e.g. a humanised recombinant antibody. The
antibody is preferably an antibody directed against the human T cell surface receptor TCR
25 V β 5.2/5.3 (the method for constructing such an antibody is described in WO 95/16038 and
the description of such methods is hereby incorporated by reference) , and is more
preferably an IgG, IgG1 or IgG/ κ . The antibody is most preferably the antibody produced
by the cell line deposited on June 22, 1995 under the Budapest treaty as ATCC (CRL
11949) [herein this antibody is referred to as 'TM27'] or is one comprising the following
30 TM27 V κ sequence:

1 DIQMTQSPSSLSASVGDRVTITCSASQGISNYLNWYQQTPGKAPKLLIYY 50

51 TSSLHSGVPSRFSGSGSGTDYFTISSLQPEDLATYYCQQYSKLPRTFGQ 100

5

101 GTKLQIT 107,

and further comprises an amino acid sequence selected from the group consisting of the
TM27 VH amino acid sequence:

10

1 QVQLQESGPGGLVRPSQTLSTCTVSGFSLTAYGVNWVRQPPGRGLEWLGM 50

51 IWGDGNTDYNSALKSRVTMLKDTSKNQFSLRLSSVTAADTAVYYCARDRV 100

15

101 TATLYAMDYWGQGSLVTVSS 120,

the TM27 VH sequence wherein amino acid residue 48 is replaced with isoleucine (I),

the TM27 VH sequence wherein amino acid residues 78 and 79 are valine (V) and

20

phenylalanine (F),

the TM27 VH sequence above wherein amino acid residues 67 to 70 VTML are replaced
with LSIS respectively and amino acid 73 is an asparagine (N),

25

the TM27 VH sequence wherein amino acid residue 92 is an arginine (R).

The present invention also provides for the use of formulations of the present invention in
medical therapy and particularly for the treatment of autoimmune disease and further
particularly in the therapy of multiple sclerosis.

30

In preferred embodiments of the present invention the formulation has a pH in the range 5.5 to 6.5 and is most preferably pH 5.5. The pH may be altered using any pharmaceutically acceptable acid or alkali.

- 5 The formulation of the present invention may be prepared under aseptic conditions, leading to a sterile formulation.

The invention will now be illustrated by reference to the following examples which are in no way intended to be limiting of the scope of the invention described herein.

EXAMPLES

The antibody assayed in the following examples is TM27 which is a humanised antibody
5 (IgG1) produced in Chinese hamster ovary (CHO) cells by recombinant technology.

The bulk batches of TM27 used were purified by protein-A affinity chromatography.
The TM27 preparations were prepared from two different TM27 bulk solutions. One was
10 10.8 mg TM27 /ml in 10 mmol/l citrate buffer pH 5.5 and the other was 11.0 mg TM27 /ml
in 10 mmol/l phosphate buffer pH 6.5. The bulk solutions had sodium chloride added to
make them isotonic.

The TM27 preparations used in this study were prepared under aseptic conditions. The
batches were protected from air with nitrogen during the manufacturing and filling
15 processes. Eight batches with different compositions were prepared using the buffers
described.

For manufacturing purposes, TM27 bulk solution was diluted with the appropriate buffer to
a concentration of 1 mg/ml TM27 by gentle mixing, while avoiding foaming. The
20 manufactured solutions were filtered through a sterile 0.22 µm MILLEX-GV filter directly
into 10 ml sterile glass vials. Filling was performed from the bottom of the vials under
nitrogen protection.

The solutions were filled into 10 ml injection vials of neutral Type I glass (Ph Eur), 1
25 ml/vial. Bromobutyl rubber stoppers (FM 257) were used and the vials were sealed with
aluminium capsules.

The batches were stored under the following conditions: +5 °C/ambient humidity and +25
°C/30 % relative humidity. All the vials were stored upright. All examples contain
30 antibody at 1 mg/ml.

<u>Example 1: 10mmol/l citrate, pH 5.5</u>	<u>amount (mg)</u>
Citric acid monohydrate for parenteral use	0.387
Sodium citrate dihydrate for parenteral use	2.400
5 Sodium chloride for aseptic preparation	8.4
Water for injection	to 1 ml

Example 2: 5 mmol/l citrate ,pH 5.5

Citric acid monohydrate for parenteral use	0.194
Sodium citrate dihydrate for parenteral use	1.200
Sodium chloride for aseptic preparation	8.69
Water for injection	to 1 ml

Example 3: 8 mmol/l citrate, pH 5.5

Citric acid monohydrate for parenteral use	0.310
Sodium citrate dihydrate for parenteral use	1.920
Sodium chloride for aseptic preparation	8.52
Water for injection	to 1 ml

Example 4: 12 mmol/l citrate, pH 5.5

Citric acid monohydrate for parenteral use	0.464
Sodium citrate dihydrate for parenteral use	2.88
Sodium chloride for aseptic preparation	8.28
Water for injection	to 1 ml

Example 5: 15 mmol/l citrate, pH 5.5

Citric acid monohydrate for parenteral use	0.581
Sodium citrate dihydrate for parenteral use	3.600
Sodium chloride for aseptic preparation	8.11
Water for injection	to 1 ml

Example 6: 18 mmol/l citrate, pH 5.5

Citric acid monohydrate for parenteral use	0.697
Sodium citrate dihydrate for parenteral use	4.320
Sodium chloride for aseptic preparation	7.93
Water for injection	to 1 ml

Example 7: 20 mmol/l citrate, pH 5.5

Citric acid monohydrate for parenteral use	0.774
Sodium citrate dihydrate for parenteral use	4.800
Sodium chloride for aseptic preparation	7.82
Water for injection	to 1 ml

Example 8 (pH 5.5)

Citric acid monohydrate for parenteral use	0.387 mg
Sodium citrate dihydrate for parenteral use	2.400 mg
Sodium chloride for aseptic preparation	8.4 mg

Polysorbat 80 (Tween 80)

0.2 mg

Water for injection

to 1 ml

- 5 The formulations were studied over a 24 month period.

The results clearly showed that storage temperature, buffer composition and pH influence the stability of TM27. The best stability is achieved at low storage temperature (+5 °C).

- The formulations exemplified in examples 1-7 were stable for 24 months whereas the
10 formulation in example 8 was stable for 12 months.

CLAIMS.

1. An isotonic pharmaceutical formulation comprising an IgG antibody and a buffer,
5 wherein the antibody is present at from 0.5 mg/ml to 10 mg/ml, the buffer is a citrate
buffer present at 5mmol/l to 20mmol/l and the pH of the formulation is 5.3 to 7.2.
2. A formulation according to claim 1, wherein the pH is 5.5 to 6.5.
- 10 3. A formulation according to claim 1, wherein the pH is 5.5.
4. A formulation according to any one of claims 1 to 3, wherein the citrate is present at
7.5mmol/l to 15mmol/l.
- 15 5. A formulation according to any one of claims 1 to 4, wherein the citrate is present at
10mmol/l.
6. A formulation according to any one of claims 1 to 5, wherein the antibody is an IgG1.
- 20 7. A formulation according to claim 6, wherein the antibody is an IgG1/ κ .
8. A formulation according to any one of the preceding claims, wherein the antibody is a
recombinant antibody.
- 25 9. A formulation according to claim 8, wherein the antibody is a humanised recombinant
antibody.
10. A formulation according to claim 9, wherein the antibody is directed against the human
T cell surface receptor TCR V β 5.2/5.3.

11. A formulation according to claim 10, wherein the antibody is produced by the cell line with the deposition number CRL 11949.

12. A formulation according to claim 11, wherein the antibody comprises the TM27 V_K amino acid sequence:

1 DIQMTQSPSSLSASVGDRVTITCSASQGISNYLNWYQQTPGKAPKLLIYY 50

51 TSSLHSGVPSRFSGSGSGTDYFTISSLPEDIATYYCQQYSKLPRTFGQ 100

101 GTKLQIT 107,

and further comprises an amino acid sequence selected from the group consisting of the TM27 V_H amino acid sequence:

1 QVQLQESGPGGLVRPSQTLSTCTVSGFSLTAYGVNWVRQPPGRGLEWLGM 50

51 IWGDGNTDYN SALKSRVTMLKDT SKNQFSLRLSSVTAADTAVYYCARDRV 100

101 TATLYAMDYWGQGS LVTVSS 120,

the TM27 V_H sequence wherein amino acid residue 48 is replaced with isoleucine (I),

the TM27 V_H sequence wherein amino acid residues 78 and 79 are valine (V) and phenylalanine (F),

the TM27 V_H sequence above wherein amino acid residues 67 to 70 VTML are replaced with LSIS respectively and amino acid 73 is an asparagine (N),

the TM27 V_H sequence wherein amino acid residue 92 is an arginine (R).

13. An isotonic pharmaceutical formulation comprising the antibody TM27 and a buffer,
wherein the antibody is present at 0.5 mg/ml to 10 mg/ml, the buffer is a citrate buffer
5 present at 5mmol/l to 20mmol/l and the pH of the formulation is 5.3 to 7.2.
14. A formulation according to any one of claims 1 to 13, which is a sterile formulation.
15. A process for the preparation of an isotonic pharmaceutical formulation according to
10 any one of claims 1 to 14, comprising incorporation of the antibody in an isotonic
medium wherein the antibody is present at from 0.5 mg/ml to 10 mg/ml, the buffer is a
citrate buffer present at 5mmol/l to 20mmol/l and the pH of the formulation is 5.3 to
7.2.
16. A formulation according to any one of the previous claims, for use in medical therapy.
17. A formulation according to any one of claims 1 to 14, for use in the therapy of an
autoimmune disease.
- 20 18. A formulation according to any one of claims 1 to 14, for use in the therapy of multiple
sclerosis.
19. Use of a formulation according to any one of claims 1 to 14, in the preparation of a
medicament for use in the therapy of an autoimmune disease.
- 25 20. Use of a formulation according to any one of claims 1 to 14, in the preparation of a
medicament for use in the therapy of multiple sclerosis.
21. A method for improving the storage of an antibody comprising formulating the
30 antibody in a formulation as claimed in any one of claims 1 to 14.

WO 99/37329

PCT/SE99/00049

SEQUENCE LISTING

<110> Lundquist, Tomas

<120> Sequence Listing

<130> 3526/00000

<140> 00/000,000

<141> 1998-11-25

<150> 00/000,000

<151> 1998-11-24

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PCT/SE99/00049

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30

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35

40

45

Tyr Tyr Thr Ser Ser Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly

50

55

60

Ser Gly Ser Gly Thr Asp Tyr Thr Phe Thr Ile Ser Ser Leu Gln Pro

65

70

75

80

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PCT/SE99/00049

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Lys Leu Pro Arg

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WO 99/37329

PCT/SE99/00049

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20

25

30

Gly Val Asn Trp Val Arg Gln Pro Pro Gly Arg Gly Leu Glu Trp Leu

35

40

45

Gly Met Ile Trp Gly Asp Gly Asn Thr Asp Tyr Asn Ser Ala Leu Lys

50

55

60

Ser Arg Val Thr Met Leu Lys Asp Thr Ser Lys Asn Gln Phe Ser Leu

65

70

75

80

Arg Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala

85

90

95

Arg Asp Arg Val Thr Ala Thr Leu Tyr Ala Met Asp Tyr Trp Gly Gln

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WO 99/37329

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Gly Val Asn Trp Val Arg Gln Pro Pro Gly Arg Gly Leu Glu Trp Ile

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Gly Met Ile Trp Gly Asp Gly Asn Thr Asp Tyr Asn Ser Ala Leu Lys

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60

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Ser Arg Val Thr Met Leu Lys Asp Thr Ser Lys Asn Gln Phe Ser Leu

65

70

75

80

Arg Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala

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WO 99/37329

PCT/SE99/00049

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Gly Val Asn Trp Val Arg Gln Pro Pro Gly Arg Gly Leu Glu Trp Leu

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Gly Met Ile Trp Gly Asp Gly Asn Thr Asp Tyr Asn Ser Ala Leu Lys

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Ser Arg Val Thr Met Leu Lys Asp Thr Ser Lys Asn Gln Val Phe Leu

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Arg Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala

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Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Ala Tyr

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Ser Arg Leu Ser Ile Ser Lys Asp Asn Ser Lys Asn Gln Phe Ser Leu

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WO 99/37329

PCT/SE99/00049

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Gly Val Asn Trp Val Arg Gln Pro Pro Gly Arg Gly Leu Glu Trp Leu

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Gly Met Ile Trp Gly Asp Gly Asn Thr Asp Tyr Asn Ser Ala Leu Lys

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Ser Arg Val Thr Met Leu Lys Asp Thr Ser Lys Asn Gln Phe Ser Leu

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WO 99/37329

PCT/SE99/00049

Arg Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Arg Tyr Tyr Cys Ala

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90

95

Arg Asp Arg Val Thr Ala Thr Leu Tyr Ala Met Asp Tyr Trp Gly Gln

100

105

110

Gly Ser Leu Val Thr Val Ser Ser

115

120

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 99/00049

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 39/395

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)

IPC6: A61K

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

SE,DK,FI,NO classes as above

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

WPI, BIOSIS, MEDLINE, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9311794 A1 (XOMA CORPORATION), 24 June 1993 (24.06.93), See especially page 34, lines 3-15	1,2,4,5, 14-21
Y	--	1-18
Y	WO 9516038 A2 (T CELL SCIENCES, INC.), 15 June 1995 (15.06.95), See especially abstract, claim 2 and page 60, lines 1-24	6-10,12-13, 17-20
Y	WO 9011091 A1 (CENTOCOR, INC.), 4 October 1990 (04.10.90), See abstract and claims 1-3	1-18
	--	

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

☒ See patent family 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

"I" 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 understand the principle or theory underlying the invention

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

31 March 1999

20 -04- 1999

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/00049

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0531539 A1 (MITSUI TOATSU CHEMICALS, INC.), 17 March 1993 (17.03.93), See claims 2 and 3 --	1,2
A	WO 8911298 A1 (CENTOCOR, INC.), 30 November 1989 (30.11.89) -- -----	

INTERNATIONAL SEARCH REPORT
Information on patent family members

02/03/99

International application No.

PCT/SE 99/00049

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9311794 A1	24/06/93	CA 2103887 A	14/06/93
		EP 0571613 A	01/12/93
		JP 6506362 T	21/07/94
		US 5766886 A	16/06/98
		US 5770196 A	23/06/98
		US 5821123 A	13/10/98
		US 5869619 A	09/02/99
WO 9516038 A2	15/06/95	AU 699249 B	26/11/98
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		EP 0737250 A	16/10/96
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		WO 9215331 A	17/09/92

02/03/99

PCT/SE 99/00049

Form PCT/ISA/210 (patent family annex) (July 1992)

Anexo 1

(19) **United States**

(12) Patent Application Publication **(10) Pub. No.: US 2005/0175611 A1**
Mahler et al. **(43) Pub. Date: Aug. 11, 2005**

(54) **PHARMACEUTICAL PREPARATION
COMPRISING AN ANTIBODY AGAINST THE
EGF RECEPTOR**

(60) Provisional application No. 60/543,287, filed on Feb. 11, 2004.

(76) Inventors: **Hanns-Christian Mahler, Wiesbaden (DE); Robert Mueller, (US)**

Nov. 26, 2003 (DE)..... 1035521.0

**MILLEN, WHITE, ZELANO & BRANIGAN,
P.C.**

(51) Int. Cl.⁷ A61K 39/395; A61K 31/4172;
A61K 31/198

SUITE 1400

ARLINGTON, VA 22201 (US)

(52) U.S. Cl. 424/145.1; 514/400

(57) **ABSTRACT**

(21) Appl. No.: 10/996,597

(22) Filed: Nov. 26, 2004

The invention relates to an aqueous pharmaceutical preparation comprising an antibody against endothelial growth factor receptor (EGF receptor). The preparation has increased storage stability, even at elevated temperatures, and can be used for the treatment of tumours.

PHARMACEUTICAL PREPARATION COMPRISING AN ANTIBODY AGAINST THE EGF RECEPTOR

[0001] This application claims the benefit of the filing date of U.S. Provisional Application Ser. No.60/543,287 filed Feb. 11, 2004 which is incorporated by reference herein.

[0002] The present invention relates to a stable pharmaceutical preparation comprising an antibody which is directed against the epidermal growth factor receptor (EGFR), and to the preparation and use thereof.

[0003] Various in vitro and in vivo studies have shown that blockage of EGFR by antibodies acts against tumours at various levels, for example by inhibiting cancer cell proliferation, reducing tumour-mediated angiogenesis, inducing cancer cell apoptosis and increasing the toxic effects of radiotherapy and conventional chemotherapy.

[0004] MAB c225 (INN: cetuximab) is a clinically proven antibody which binds to the EGF receptor. Cetuximab is a chimeric antibody whose variable regions are of murine origin and whose constant regions are of human origin. Cetuximab was described for the first time by Naramura et al., *Cancer Immunol. Immunotherapy* 1993, 37: 343-349 and in WO 96/40210 A1.

[0005] MAB 425 is an originally murine antibody which is directed against EGFR which is overexpressed in tumour cells, in particular A431 carcinoma cells. Its humanised and chimeric forms are disclosed, for example, in EP 0 531 472 A1; Kettleborough et al., *Protein Engineering* 1991, 4: 773-783; Bier et al., *Cancer Chemother. Pharmacol.* 2001, 47: 519-524; Bier et al., *Cancer Immunol. Immunother.* 1998, 46: 167-173. EMD 72000 (h425) is a form of MAB 425 which is in clinical phase I/II and whose constant region is composed of a κ and a human γ -1 chain.

[0006] Human anti-EGFR antibodies can be provided by XenoMouse technology, as described in WO 91/10741 A1, WO 94/02602 A1 and WO 96/33735 A1. A specific antibody which has been produced by this technology and is currently undergoing clinical trials is ABX-EGF (Abgenix, *Crit. Rev. Oncol. Hematol.* 2001, 38: 17-23; *Cancer Research* 1999, 59: 1236-43).

[0007] Further antibodies directed against EGFR are described, for example, in EP 0 586 002 B1 and in *J. Natl. Cancer Inst.* 1993, 85: 27-33 (MAB 528).

[0008] Like other antibodies, anti-EGFR antibodies are also applied parenterally as a solution for therapeutic use. A particular problem of solutions comprising these antibodies is their tendency toward aggregation and the formation of protein multimers. In the case of reducible multimers, this can be attributed to unintentional intermolecular disulfide bridge formation through interaction between approaching moieties. Hydrophobic interactions and the consequent formation of non-reducible multimers are also possible. Furthermore, deamidation reactions, which subsequently result in protein degradation reactions, also occur. The denaturing reactions described occur, in particular, on storage at elevated temperature or during shear stresses, as occur, for example, during transport.

[0009] As a consequence of the said aggregation tendency, product precipitation occurs during storage of antibody solutions, meaning that reproducible withdrawal from the

container containing the solution is doubtful. In addition, emboli can occur on parenteral administration of particle-containing solution. This has the consequence that the administration of the anti-EGFR antibodies to the patient in the requisite dose in each case is not always guaranteed in a reproducible manner by means of antibody solutions, and the administration cannot take place with the requisite reliability.

[0010] Although filtration before injection enables the aggregates to be held back, this method, however, comprises an additional step and is therefore complex and not very suitable for clinical practice. In addition, the problem of dose reproducibility remains unsolved, since an unknown fraction of antibodies is in each case separated off from the solution, and particle formation after filtration continues to represent a safety risk.

[0011] A common method for the stabilisation of monoclonal antibodies is freeze-drying of solutions comprising antibodies and auxiliaries. However, lyophilisation is very time- and energy-consuming and thus expensive. In addition, the lyophilisate must first be reconstituted before administration. EP 0 073 371 describes preparations for intravenous administration which comprise immunoglobulins which have a pH of from 3.5 to 5.0 for stabilisation. However, such low pH values result in undesired incompatibility reactions at the injection point.

[0012] U.S. Pat. No. 6,171,586 B1 discloses the use of an acetate buffer pH 4.48 to 5.5, a surfactant and a polyol in an aqueous formulation of antibodies, with NaCl for isotonicity modification being excluded. Owing to the lack of isotonicity modification, incompatibility reactions at the injection point may likewise occur.

[0013] As examples of further formulations comprising specific antibodies, reference may be made at this point to EP 0 280 358, EP 0 170 983 and U.S. Pat. No. 5,945,098.

[0014] Of these, EP 0 280 358 describes the addition of dextran to an antibody solution for stabilisation against certain hormones, where stability was achieved over nine months.

[0015] EP 0 170 983 describes the stabilisation of a thermolabile monoclonal antibody by heating together with hydrolysed ovalbumin, as a result of which the antibody was still stable after storage for 7 days at 45° C. However, the addition of proteins of other species to formulations intended for parenteral administration is undesired owing to the problems associated therewith, in particular their possible antigenicity.

[0016] U.S. Pat. No. 5,945,098 discloses the use of glycine, polysorbate 80 and polyethylene glycol for the stabilisation of an aqueous solution of immunoglobulin G.

[0017] DE 10133394 A1 discloses the use of a phosphate buffer in the range from pH 6 to pH 8 and a polyoxyethylene sorbitan fatty acid ester for the stabilisation of an aqueous solution of the antibody cetuximab. Although this significantly reduces the formation of visible aggregates, the chemical stability, in particular under stress conditions, is significantly impaired. Furthermore, the formulation does not exhibit stability to (extreme) thermal stress, for example long-term storage at 40° C.

[0018] The object of the invention was to find an aqueous formulation specifically for the antibodies directed against EGFR which is suitable for parenteral administration, is well tolerated and is stable on storage at room temperature over at least 24 months. The storage stability should also be retained in the case of shear forces acting during transport and under modified climatic conditions, in particular at elevated temperature and atmospheric humidity. Furthermore, the formulation should have a simple structure and should not comprise any auxiliaries which are dubious from a toxicological point of view.

[0019] Surprisingly, a formulation which meets these requirements has been found in the form of a solution which, in addition to an antibody directed against epidermal growth factor (anti-EGFR antibody), comprises a buffer, an amino acid and a surfactant. The present invention therefore relates to an aqueous pharmaceutical preparation which, in addition to an anti-EGFR antibody, comprises a buffer, an amino acid and a surfactant.

[0020] For the purposes of the invention, an aqueous preparation is one in which at least some of the solvent present consists of water. Further solvent constituents which may be present are all solvents which are suitable for parenteral use, in particular alcohols, such as, for example, ethanol, propanol, propanediol or glycerol. The aqueous preparation preferably comprises, as solvent, water or ethanol/water mixtures; the solvent particularly preferably consists of water.

[0021] The antibody present can be any anti-EGFR antibody, in particular the murine, humanised or chimeric antibodies mentioned at the outset and the human anti-EGFR antibodies which have been and can be prepared by means of the said XenoMouse technology. Preference is given to the anti-EGFR antibody cetuximab or EMD 72000 or one of the murine, humanised or chimeric antibody analogues corresponding thereto. Particular preference is given to aqueous preparations which comprise cetuximab or EMD 72000 as antibody.

[0022] The anti-EGFR antibody may be present in the formulation according to the invention in a concentration of from 0.1 mg/ml to 50 mg/ml, preferably from 2 mg/ml to 10 mg/ml, particularly preferably about 5 mg/ml.

[0023] Buffers which can be employed are basically all physiologically tolerated substances which are suitable for setting the desired pH, such as, for example, citrate salts, acetate salts, histidine salts, succinate salts, malate salts, phosphate salts or lactate salts, and/or the respective free acids or bases thereof, as well as mixtures of the various salts and/or acids or bases thereof. The buffer preferably consists of one or more citrate salt(s), acetate salt(s), histidine salt(s), succinate salt(s), malate salt(s), phosphate salt(s) or lactate salt(s) and/or the respective free acid(s) or base(s) thereof or a mixture of one or more of the various salts and/or the acid(s) or base(s) thereof. The term mixture here covers both mixtures of different salts of the same acid, such as, for example, mixtures of different citrate salts, and mixtures of salts of different acids, such as, for example, mixtures of citrate and acetate salts. The buffer preferably consists of one or more citrate salt(s) and/or the free acid thereof (for example citric acid, citric acid monohydrate, trisodium citrate dihydrate, tripotassium citrate monohydrate), acetate salt(s) and/or the free acid thereof (for example acetic acid,

sodium acetate, sodium acetate trihydrate) or L-histidine and/or an acid-addition salt thereof, such as, for example, L-histidine monohydrochloride monohydrate. The preparation according to the invention advantageously comprises the buffer in a concentration of from 10 to 100 mmol/l, preferably from 2 to 20 mmol/l, particularly preferably about 10 mmol/l.

[0024] The pH of the preparation is in the range from 5.0 to 6.0, preferably from 5.2 to 5.8, particularly preferably about 5.5.

[0025] The preparation according to the invention is physiologically well tolerated, can be prepared easily, can be dispensed precisely and is stable with respect to assay, decomposition products and aggregates over the duration of storage, during repeated freezing and thawing processes and mechanical stress. It is stable on storage over a period of at least 3 months to a period of 4 years at refrigerator temperature (2-8° C). Surprisingly, the preparation according to the invention is also stable on storage over a period of up to 2 years at elevated temperatures and higher atmospheric humidity levels, for example at a temperature of 25° C. and 60% relative atmospheric humidity, or over a period of 3 months at a temperature of 40° C. and 75% relative atmospheric humidity.

[0026] The amino acid present in the preparation can be basic amino acids, such as, for example, arginine, histidine, ornithine, lysine, or neutral amino acids, such as, for example, glycine, methionine, isoleucine, leucine and alanine, or aromatic amino acids, such as, for example, phenylalanine, tyrosine or tryptophan. Basic amino acids are preferably employed in the form of their inorganic salts (advantageously in the form of the hydrochloric acid salts, i.e. as amino acid hydrochlorides). The amino acid employed is preferably in each case the L-form. The amino acid present in the preparation according to the invention is particularly preferably L-arginine, glycine or L-methionine.

[0027] The preparation comprises the amino acid in a concentration of from 2 to 200 mmol/l, preferably from 50 to 150 mmol/l, particularly preferably about 100 mmol/l.

[0028] Surfactants which can be employed are all surfactants usually used in pharmaceutical preparations, preferably polyethylene sorbitan fatty acid esters and polyoxyethylene-polyoxypropylene copolymers. Polyethylene sorbitan fatty acid esters are also known under the trade name 'Tween'. Suitable polyethylene sorbitan fatty acid esters are, in particular, polyoxyethylene (20) sorbitan monolaurate, polyoxyethylene (20) sorbitan monopalmitate and polyoxyethylene (20) sorbitan monostearate. Preference is given to polyoxyethylene (20) sorbitan monolaurate and polyoxyethylene (20) sorbitan monooleate, particular preference being given to polyoxyethylene (20) sorbitan monooleate. Polyoxyethylene-polyoxypropylene copolymers are also known under the trade name Poloxamer.

[0029] A particularly preferred polyoxyethylene-polyoxypropylene copolymer is Poloxamer 407 (CAS 9003-11-6).

[0030] The surfactants may be present in the formulation in a concentration of from 0.001 % to 1.0% by weight. If polyoxyethylene sorbitan fatty acid esters are present as surfactants, these are preferably present in an amount of from 0.005 to 0.1 % by weight, particularly preferably in an amount of about 0.01 % by weight. If polyoxyethylene-

polyoxypropylene copolymers are present, these are preferably present in an amount of from 0.01 to 0.5% by weight, particularly preferably about 0.1% by weight.

[0031] In order to increase the tolerability on parenteral administration, the osmolality is preferably in the isotonic range, i.e. at an osmolality of from about 250 to 350 mOsmol/kg. The preparation can then be administered directly intravenously, intraarterially and also subcutaneously substantially without pain.

[0032] According to an advantageous embodiment, the preparation according to the invention therefore additionally comprises an isotonicity modifier, preferably a physiologically tolerated salt, such as, for example, sodium chloride or potassium chloride, or a physiologically tolerated polyol, such as, for example, glucose or glycerol, in a concentration necessary for isotonicity modification. The invention therefore furthermore relates to an aqueous preparation comprising an anti-EGFR antibody, a buffer, an amino acid, a surfactant and an isotonicity modifier in a concentration necessary for isotonicity modification. Sodium chloride is particularly preferably present as isotonicity modifier.

[0033] In addition, the solutions according to the invention may comprise further physiologically tolerated auxiliaries, such as, for example, antioxidants, such as ascorbic acid or glutathione, preservatives, such as phenol, m-cresol, methyl- or propylparaben, chlorobutanol, thiomersal or benzalkonium chloride, polyethylene glycols (PEG), such as PEG 400, PEG 3000, 3350, 4000 or 6000, disaccharides, such as trehalose or saccharose, or cyclodextrins, such as hydroxypropyl- β -cyclodextrin, sulfobutylethyl- β -cyclodextrin, α -cyclodextrin or γ -cyclodextrin.

[0034] According to a particularly advantageous embodiment of the invention, the aqueous preparation comprises about 5 mg/ml of cetuximab or EMD 72000, about 10 mmol/l of citrate or histidine buffer having a pH of about 5.5, about 100 mmol/l of glycine, arginine or L-methionine, about 100 mmol/l of sodium chloride and about 0.01% of polyoxyethylene (20) sorbitan monooleate.

[0035] The aqueous preparation can be prepared by adding the said auxiliaries to a solution comprising the anti-EGFR antibody. To this end, defined volumes of stock solutions comprising the said further auxiliaries in defined concentration are advantageously added to a solution having a defined concentration of the anti-EGFR antibody, as obtained from its preparation, and the mixture is, if desired, diluted to the pre-calculated concentration with water or buffer solution. Alternatively, the auxiliaries can also be added as solids to the starting solution comprising the anti-EGFR antibody. If the anti-EGFR antibody is in the form of a solid, for example in the form of a lyophilisate, the preparation according to the invention can be prepared by firstly dissolving the respective antibodies in water or an aqueous solution comprising one or more of the further auxiliaries, and subsequently adding the amounts required in each case of stock solutions comprising the further auxiliaries, the further auxiliaries in solid form and/or water. The anti-EGFR antibody can advantageously also be dissolved directly in a solution comprising all further auxiliaries.

[0036] One or more of the auxiliaries present in the preparation according to the invention may advantageously already have been added during or at the end of the process

for the preparation of the particular EGFR antibody. This can preferably be carried out by dissolving the anti-EGFR antibody directly in an aqueous solution comprising one, more than one or all of the further auxiliaries in the final step of the purification carried out after its preparation. In order to prepare the preparation, the respective further ingredient(s) then need only be added in a smaller amount in each case and/or not added at all. It is particularly preferred for the respective ingredient to be dissolved directly in an aqueous solution comprising all further auxiliaries in the final step of the purification carried out after its preparation.

[0037] If the solution comprising the respective antibody and the auxiliaries does not yet have the desired pH, this is set by addition of an acid or base, preferably using the acid or base already present in the buffer system. This is followed by sterile filtration.

[0038] The aqueous preparation according to the invention can advantageously be employed for the treatment of tumour diseases.

[0039] The examples explain the invention without being restricted thereto.

[0040] Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

[0041] In the foregoing and in the following examples, all temperatures are set forth uncorrected in degrees Celsius and, all parts and percentages are by weight, unless otherwise indicated.

EXAMPLE 1

COMPARATIVE EXAMPLE 1

[0042] Aqueous solution comprising:

[0043] 2 mg/ml of cetuximab

[0044] 10 mmol/l of sodium phosphate buffer pH 7.2

[0045] 145 mmol/l of sodium chloride

[0046] The preparation is carried out by mixing defined volumes of aqueous solutions comprising the respective auxiliaries in defined concentration. The following solutions are used:

[0047] Solution A (active ingredient solution) comprising:

[0048] 18 mg/ml of cetuximab

[0049] 10 mmol/l of sodium phosphate buffer pH 7.2

[0050] (consisting of 2.07 g/l of disodium hydrogenphosphate 7-hydrate and 0.31 g/l of sodium dihydrogenphosphate monohydrate)

[0051] 145 mmol/l of sodium chloride

[0052] (The solution is obtained by re-buffering the active ingredient against solution B with the aid of tangential flow filtration in the final step of the active-ingredient purification taking place after preparation thereof.)

[0053] Solution B (buffer/salt solution)

[0054] Corresponds to solution A, but comprises no active ingredient.

[0055] For the preparation of Comparative Solution 1, 1.11 parts by volume of solution A and 8.89 parts by volume of solution B are combined with one another.

[0056] The solution prepared is filtered using a sterile filter before transfer and transferred into injection vials. The injection vials are subsequently sealed with stoppers and crimped.

EXAMPLE 2

COMPARATIVE EXAMPLE 2

[0057] Aqueous solution comprising:

[0058] 2 mg/ml of cetuximab

[0059] 10 mmol/l of sodium phosphate buffer pH 7.2

[0060] 145 mmol/l of sodium chloride

[0061] 0.01% by weight of polyoxyethylene (20) sorbitan monooleate

[0062] The preparation is carried out by mixing defined volumes of aqueous solutions comprising the respective ingredients in defined concentration. Besides solution A, the following solution is used.

[0063] Solution C (buffer/salt solution comprising polyoxyethylene (20) sorbitan monooleate)

[0064] Corresponds to solution B, but additionally comprises 0.0125% by weight of polyoxyethylene (20) sorbitan monooleate.

[0065] For the preparation of comparative solution 2, 1.11 parts by volume of solution A and 8.89 parts by volume of solution C are combined with one another.

[0066] The solution prepared is filtered using a sterile filter before transfer and transferred into injection vials. The injection vials are subsequently sealed with stoppers and crimped.

EXAMPLE 3

Formulation According to the Invention

[0067] 5 mg/ml of cetuximab

[0068] 10 mmol/l of citrate buffer pH 5.5

[0069] 100 mmol/l of glycine

[0070] 100 mmol/l of sodium chloride

[0071] 0.01% by weight of polyoxyethylene (20) sorbitan monooleate

[0072] The preparation is carried out by mixing defined volumes of aqueous solutions comprising the respective ingredients in defined concentrations.

[0073] Solution D (active ingredient solution in a citrate buffer)

[0074] 16 mg/ml of cetuximab

[0075] 10 mmol/l of citrate buffer pH 5.5

[0076] (consisting of 2.1014 g/l of citric acid monohydrate)

[0077] (The solution is obtained by re-buffering the active ingredient against solution E with the aid of tangential flow filtration in the final step of the active-ingredient purification taking place after preparation thereof.)

[0078] Solution E (buffer solution):

[0079] Corresponds to solution D, but comprises no active ingredient.

[0080] Solution F (buffer/salt solution):

[0081] Corresponds to solution E, but comprises

[0082] 145.5 mmol/l of glycine,

[0083] 145.5 mmol/l of sodium chloride and

[0084] 0.015% by weight of polyoxyethylene (20) sorbitan monooleate.

[0085] For the preparation of the formulation according to the invention, 3.125 parts by volume of solution D and 6.875 parts by volume of solution F are combined with one another.

[0086] The solution prepared is filtered using a sterile filter before transfer and transferred into injection vials. The injection vials are subsequently sealed with stoppers and crimped.

EXAMPLE 4

[0087] The following solutions are prepared analogously to the method of the examples described above:

[0088] Example 4.1, solution comprising:

[0089] 5 mg/ml of cetuximab

[0090] 100 mmol/l of glycine

[0091] 0.01 % by weight of polyoxyethylene (20) sorbitan monooleate

[0092] 10 mmol/l of citrate buffer pH 5.5

[0093] (consisting of 2.9410 g/l of trisodium citrate dihydrate)

[0094] Example 4.2, solution comprising:

[0095] 5 mg/ml of cetuximab

[0096] 100 mmol/l of glycine

[0097] 100 mmol/l of sodium chloride

[0098] 0.01 % by weight of polyoxyethylene (20) sorbitan monooleate

[0099] 10 mmol/l of citrate buffer pH 5.5

[0100] (consisting of 2.1014 g/l of citric acid monohydrate)

[0101] Example 4.3, solution comprising:

[0102] 5 mg/ml of EMD 72000

[0103] 100 mmol/l of glycine

[0104] 100 mmol/l of sodium chloride

[0105] 0.01 % by weight of polyoxyethylene (20) sorbitan monooleate

- [0106] 10 mmol/l of citrate buffer pH 5.5
- [0107] (consisting of 2.1014 g/l of citric acid monohydrate)
- [0108] Example 4.4, solution comprising:
- [0109] 5 mg/ml of cetuximab
- [0110] 100 mmol/l of L-methionine
- [0111] 0.01 % by weight of polyoxyethylene (20) sorbitan monooleate
- [0112] 10 mmol/l of citrate buffer pH 5.5
- [0113] (consisting of 2.1014 g/l of citric acid monohydrate)
- [0114] Example 4.5, solution comprising:
- [0115] 5 mg/ml of cetuximab
- [0116] 100 mmol/l of glycine
- [0117] 0.01 % by weight of polyoxyethylene (20) sorbitan monooleate
- [0118] 10 mmol/l of acetate buffer pH 5.5
- [0119] (consisting of 1.3608 g/l of sodium acetate trihydrate)
- [0120] Example 4.6, solution comprising:
- [0121] 5 mg/ml of cetuximab
- [0122] 100 mmol/l of glycine
- [0123] 0.01% by weight of polyoxyethylene (20) sorbitan monooleate
- [0124] 10 mmol/l of histidine buffer pH 5.5
- [0125] (consisting of 2.069 g/l of L-histidine monohydrochloride monohydrate)
- [0126] Example 4.7, solution comprising:
- [0127] 5 mg/ml of cetuximab
- [0128] 100 mmol/l of glycine
- [0129] 0.01 % by weight of polyoxyethylene (20) sorbitan monolaurate

- [0130] 10 mmol/l of citrate buffer pH 5.5
- [0131] (consisting of 2.1014 g/l of citric acid monohydrate)
- [0132] Example 4.8, solution comprising:
- [0133] 5 mg/ml of cetuximab
- [0134] 100 mmol/l of glycine
- [0135] 0.1 % by weight of polyoxyethylene-polyoxypropylene copolymer 407
- [0136] (Poloxamer 407)
- [0137] 10 mmol/l of citrate buffer pH 5.5
- [0138] (consisting of 2.1014 g/l of citric acid monohydrate)

EXAMPLE 5

[0139] The stability of the formulation according to the invention was tested in a stress test. To this end, vials containing the solution according to Example 3 and, for comparative purposes, vials containing solution according to Examples 1 and 2 were stored at 25° C. and 60% relative atmospheric humidity and 40° C. and 75% relative atmospheric humidity. In addition, vials containing solutions according to Examples 1, 2 and 3 were shaken for five days in a shaking apparatus at a shaking frequency of 150 min⁻¹ at room temperature and frozen three times in succession at -20° C. and subsequently thawed again at +5° C. Before storage and after defined storage times, the vials were assessed visually with direct illumination with a cold-light source, and the absorption of the solutions at 350 nm, which represents a measure of the turbidity, was determined. In order to illustrate the influence of storage or treatment, the relative turbidity was in each case calculated relative to the starting value. Furthermore, the vials were analysed by means of HPLC gel filtration with respect to the content of cetuximab, aggregates and decomposition products.

[0140] The results of the stability investigations are shown in Table 1.

TABLE 1

Summary of the stability data of the formulation according to the invention (Example 3) and the two comparative solutions (Examples 1 and 2)

Test solution	Storage [time/conditions]	Cetuximab [%]	Aggregates [%]	Decomposition products [%]	Turbidity at $\lambda = 350$ nm	Relative turbidity at $\lambda = 350$ nm	Visual assessment
Example 1	0 weeks	99.67	0.12	0.22	0.005	1.00	Small particles, low number, clear
Example 1	8 weeks 25° C./60% R.H.	98.99	0.28	0.73	0.0081	1.62	Large particles, large number, clear
Example 1	8 weeks 40° C./	95.08	3.23	1.69	0.0235	4.70	Large particles,

TABLE 1-continued

Summary of the stability data of the formulation according to the invention (Example 3) and the two comparative solutions (Examples 1 and 2)							
Test solution	Storage [time/conditions]	Cetuximab [%]	Aggregates [%]	Decomposition products [%]	Turbidity at $\lambda = 350$ nm	Relative turbidity at $\lambda = 350$ nm	Visual assessment
	75% R.H.						large number, clear
Example 1	Shaking for 5 days at 150 rpm and RT	99.60	0.17	0.24	0.829	165.80	Very large particles, very high particle number, cloudy
Example 1	3 freeze/thaw cycles between -20° C. and $+5^{\circ}$ C.	99.68	0.14	0.18	0.0089	1.78	Large particles, high particle content, slightly cloudy
Example 2	0 weeks	99.62	0.18	0.21	0.0048	1.00	No particles, clear
Example 2	8 weeks 25° C./60% R.H.	99.02	0.28	0.70	0.0071	1.48	Small particles, low number, clear
Example 2	8 weeks 40° C./75% R.H.	93.95	4.34	1.72	0.0241	5.02	Small particles, low number, clear
Example 2	Shaking for 5 days at 150 rpm and RT	99.51	0.26	0.23	0.0075	1.56	No particles, clear
Example 2	3 freeze/thaw cycles between -20° C. and $+5^{\circ}$ C.	99.61	0.21	0.18	0.0064	1.48	No particles, clear
Example 3	0 weeks	99.72	0.15	0.14	0.018	1.00	No particles, clear
Example 3	8 weeks 25° C./60% R.H.	99.38	0.18	0.44	0.020	1.08	Small particles, low number, clear
Example 3	8 weeks 40° C./75% R.H.	98.15	0.46	1.40	0.030	1.63	Small particles, low number, clear
Example 3	Shaking for 5 days at 150 rpm and RT	99.15	0.70	0.15	0.019	1.04	No particles, clear
Example 3	3 freeze/thaw cycles between -20° C. and $+5^{\circ}$ C.	99.75	0.14	0.12	0.018	1.00	No particles, clear

[0141] The results clearly show that the formulation according to the invention has significantly increased stability compared with the comparative solutions of the prior art.

[0142] The entire disclosures of all applications, patents and publications, cited herein and of corresponding German application No.1035521.0, filed Nov. 26, 2003, and U.S. Provisional Application Ser. No. 60/543,287, filed Feb. 11, 2004 are incorporated by reference herein.

[0143] The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

[0144] From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention and, without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

1. Aqueous preparation comprising an anti-EGFR antibody, a buffer, an amino acid and a surfactant.

2. Preparation according to claim 1, characterised in that the antibody is cetuximab or EMD 72000 or one of the corresponding murine, humanised or chimeric antibody analogues.

3. Preparation according to claim 2, characterised in that the antibody is cetuximab or EMD 72000.

4. Preparation according to claim 1, characterised in that the buffer consists of one or more citrate salt(s), acetate salt(s), histidine salt(s), succinate salt(s), malate salt(s), phosphate salt(s) or lactate salt(s) and/or the respective free acid(s) or base(s) thereof or a mixture of one or more of the various salts and/or the acid(s) or base(s) thereof.

5. Preparation according to claim 4, characterised in that the buffer consists of one or more citrate salt(s) and/or the

free acid thereof, acetate salt(s) and/or the free acid thereof or L-histidine and/or an acid-addition salt thereof.

6. Preparation according to claim 1, characterised in that the amino acid is L-arginine, glycine or L-methionine.

7. Preparation according to claim 1, characterised in that the surfactant is a polyethylene sorbitan fatty acid ester or a polyoxyethylene-polyoxypropylene copolymer.

8. Preparation according to claim 7, characterised in that the polyoxyethylene sorbitan fatty acid ester surfactant is polyoxyethylene (20) sorbitan monooleate or polyoxyethylene (20) sorbitan monolaurate.

9. Preparation according to claim 7, characterised in that the surfactant is Poloxamer 407.

10. Preparation according to claim 1, characterised in that an isotonicity modifier is furthermore present in a concentration necessary for isotonicity modification.

11. Preparation according to claim 10, characterised in that the isotonicity modifier is sodium chloride.

12. Preparation according to claim 1, characterised in that it has a pH of 5-7, preferably from pH 5.2 to pH 6.0.

13. Preparation according to claim 12, characterised in that it has a pH of about 5.5.

14. Preparation according to claim 1, characterised in that it comprises about 5 mg/ml of cetuximab or EMD 72000, about 10 mmol/l of citrate or histidine buffer, about 100 mmol/l of glycine, L-arginine or L-methionine, about 100 mmol/l of sodium chloride and about 0.01% of polyoxyethylene (20) sorbitan monooleate and has a pH of about 5.5.

15. Process for the preparation of a pharmaceutical preparation according to claim 1, characterised in that an aqueous preparation comprising the anti-EGFR antibody is added to one of the said auxiliaries.

16. Use of the preparation according to claim 1 for the treatment of tumour diseases.

* * * * *

2020
Bogotá, D.C.,

Doctor:
Álvaro Correa Ordóñez
Apoderado

Oficio N°: 08870

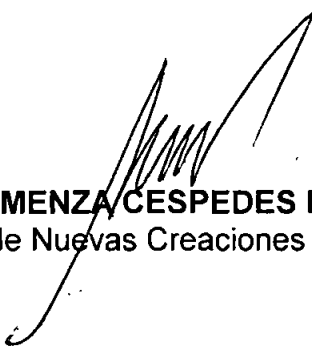
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Radicación PCT N°	08-124345
Trámite	011
Evento	378
Actuación	440
Folios	009

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por la doctora Cielo Ángela Peña Rodríguez, en su calidad de apoderada de Gynopharm S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

En cumplimiento de lo dispuesto en la citada norma, se le concede el término de sesenta (60) días hábiles siguientes a la fecha de notificación del presente oficio, para que haga valer sus argumentaciones y presente pruebas.

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
Directora de Nuevas Creaciones (C).

El anterior oficio fue notificado por fijación en lista de fecha, 16 JUL. 2010.

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