Señor
SUPERINTENDENTE DE INDUSTRIA Y C[illegible]
DIVISION DE NUEVAS CREACIONES
E. S.

Re: P1.-**ELI LILLY AND COMPANY.**-Solicitud de Patente de Invención para **"COMPOSICION FARMACEUTIC QUE COMPRENDE PEMETREXED"**.-Clase A.61.-Expediente número **01-007.346.-**

1. Me refiero a mi solicitud de patente de fecha 1 de Febrero de 2001 y al requerimiento hecho por ese Despacho notificado por fijación en lista de fecha 19 de Abril de 2001.

2. Anexos me permito presentar a usted:

(1) Copias autenticas (2) de las primeras solicitudes de patente presentadas para el invento arriba nombrado **respecto de la cual reclamo prioridad,** a saber:

(a) Copia autentica debidamente certificada de la solicitud británica número 0002691.4 de 4 de Febrero de 2000, junto con la traducción oficial, correspondiente a las legalizaciones y reivindicaciones de dicho documento;

(b) Copia autentica debidamente certificada de la solicitud británica número 0019599.0 de 9 de Agosto de 2000, junto con la traducción oficial, correspondiente a las legalizaciones y reivindicaciones de dicho documento;

(2) Copia debidamente autenticada por el Notario Sexto del Circulo de Bogotá, de los documentos que acreditan la calidad de Traductor Oficial de la señora María Mercedes Uricoechea quien elaboró la traducción de las solicitudes

estadinenses número 0002691.4 y 0019599.0, respecto de las cuales se reivindica prioridad en el presente caso;

(3) Documento que acredita el traspaso que los autores del invento de la referencia hacen a favor de mi representado de sus derechos sobre el mismo debidamente apostillado junto con su traducción oficial número 485 debidamente legalizado hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número 320300 de fecha 29 de Marzo de 2001; y

(4) Documento que acredita el traspaso que la sociedad Lilly Forschung GmbH hace a favor de mi representado, de sus derechos sobre el mismo debidamente apostillado junto con sus traducciones oficiales número 8332 y 8251 debidamente legalizadas hasta por el Ministerio de Relaciones Exteriores de Colombia bajo los números 131315 y 428354 de 30 de Abril y 3 de Mayo de 2001, respectivamente.

(5) Recibo número 19,083, expedido por la Superintendencia de Industria y Comercio, que acredita el pago de la tasa de invocación de prioridad en el presente caso.

9. Ruego a usted tomar atenta nota de lo anterior y proceder de conformidad.

Señor Superintendente,

JOSE ANTONIO LLOREDA
T.P. 10.784
Código 231

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 01 - 19,083
FECHA : MARZO 23 DE 2001

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
LLOREDA Y CIA S. A	CONSIGNACION	BANCO POPULAR	050-00110-6	2899962	23/03/2001	6,273,640.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50003-01-01 SOLICITUDES	82 INVOCACION DE UNA PRIORIDAD EN NU	100,000.00
		TOTAL : $	100,000.00

SON: CIEN MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

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

REPUBLICA DE COLOMBIA
MINISTERIO DE RELACIONES EXTERIORES

22 24

CERTIFICACION

Se hace constar que el Señor(a) MARIA MERCEDES URICOECHEA TORRES

se encuentra debidamente registrado(a) ante el Ministerio de Relaciones

Exteriores, como traductor e interprete oficial para los idiomas

Ingles - Español - Ingles, según resolución Nº 10607

de fecha 31 de Diciembre de 1981 del Ministerio de Justicia.

Se expide a los 6 dias del mes de Abril de 1983.

Atentamente,

RAFAEL HUMBERTO PEÑA FLOREZ
JEFE DE NEGOCIOS GENERALES

COMO NOTARIO DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA AUTENTICA QUE HE TENIDO A LA VISTA.
SANTAFE DE BOGOTA 24 AGO. 1998

COMO NOTARIO SEXTO ENCARGADO DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA AUTENTICA QUE HE TENIDO A LA VISTA
SANTAFE DE BOGOTA 24 NOV 1998
JUAN MANUEL BOTERO MEDINA
NOTARIO

16 JUN 1998

COMO NOTARIO SEXTO DEL CIRCULO DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA AUTENTICA QUE HE TENIDO A LA VISTA
SANTAFE DE BOGOTA 16 ENE 2001

MINISTERIO DE RELACIONES EXTERIORES

Eli Lilly
Z-1032
25

OFICINA DE PATENTES

Concept House
Cardiff Road
Newport
South Wales
NP9 1RH

El suscrito, un funcionario debidamente autorizado conforme a los Artículos 74(1) y (4) de la Ley de Desreglamentación y Contratación de 1994 para firmar y expedir certificados en nombre del Contralor General, certifico que la copia adjunta es una copia correcta de los documentos archivados originalmente con respecto a la solicitud de patente que allí se identifica.

De acuerdo con las Reglamentaciones de Patentes de 1982 (Re-registro de Compañías), si una compañía nombrada en este certificado y en los documentos adjuntos se ha vuelto a registrar según la Ley de Compañías de 1980 con el mismo nombre con el que fue registrada inmediatamente antes del re-registro, salvo la sustitución o inclusión como la última parte del nombre de las palabras "sociedad anónima" o su equivalente en galés, las referencias al nombre de la compañía y sus documentos adjuntos serán tratadas como referencias al nombre con el cual fue re-registrada.

De acuerdo con las reglas, las palabras "sociedad anónima" (o en inglés *public limited company)* pueden ser reemplazadas por las letras p.l.c, plc. P.L.C ó PLC.

El re-registro bajo la Ley de Compañías no constituye una nueva entidad legal sino simplemente somete a la compañía a ciertas normas de ley adicionales.

(FIRMA) R. MAHONEY FECHA: 17 de enero de 2001
(SELLO DE LACRE)

0002691.4 – feb 01

María Mercedes [illegible]
Res. No. 1032
Traductora Juramentada

OFICINA DE PATENTES

SOLICITUD DE PATENTE

1. Su referencia: **Z. 1032**

2. Solicitud No. **0002691.4** 04 de febrero de 2000

3. Nombre completo y código postal de cada solicitante:

Dirección: LILLY FORSCHUNG GmbH.
ESSENER STRASSE 93,
D-22419 HAMBURGO
ALEMANIA

ADP 7828999001

Si el solicitante es una entidad, indique el pais/estado de constitución:
ALEMANIA

TITULO DEL INVENTO:

COMPOSICIÓN FARMACÉUTICA

5. NOMBRE DE SU AGENTE:

Nombre del Agente: C. M. HUDSON

Dirección para notificaciones: LILLY RESEARCH CENTRE
ERL WOOD MANOR
WINDLESHAM
SURREY GU20 6PH

NO. ADP Patentes 2303001

Maria Hudson

6. Si declara prioridad de una o más patentes anteriores, indique el pais y la fecha de radicación de cada una de ellas: N/A

7. N/A

8. SI

---

9. Número de hojas radicadas (En inglés). Descripción: 6 Reivindicaciones: 2

Resumen : 1 Dibujos: 0

10. Solicitud de examen preliminar y búsqueda :

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11. Solicitamos se nos adjudique una patente con base en esta solicitud.

C.M. HUDSON, 4 de febrero de 2000

12. Nombre y teléfono del contacto en el Reino Unido Nombre y teléfono del contacto en el Reino Unido (FIRMA) C.M. HUDSON (01276) 853443

María Mercedes [illegible]
Traductora Jurament[illegible]

COMPOSICIONES FARMACÉUTICAS

REIVINDICACIONES:

1. Una composición farmacéutica que comprende:

a) un pemetrexo

b) al menos un antioxidante seleccionado del grupo compuesto por:

i) monotioglicerol

ii) L-cisteína, y

iii) ácido tioblicólico; y

c) un excipiente farmacéuticamente aceptable

2. Una composición farmacéutica según la Reivindicación 1, en donde la composición es una formulación líquida adecuada para administración parenteral.

3. Una composición farmacéutica según cualquiera de las Reivindicaciones 1 a 2, en donde el premetrexo es la sal disódica.

4. Una composición farmacéutica según cualquiera de las reivindicaciones 1 a 3, en donde el antioxidante es monotioglicerol

5. Una composición farmacéutica según cualquiera de las Reivindicaciones 1 a 4, en donde la concentración de monotioglicerol es

entre aproximadamente 1 parte por millón a aproximadamente 8 miligramos por milímetro.

6. Una composición farmacéutica según la Reivindicación 5, en donde la concentración de monotioglicerol es entre aproximadamente 1 mg/ml a aproximadamente 6 mg/ml.

7. Una composición farmacéutica según la Reivindicación 6, en donde la concentración de monotioglicerol es entre aproximadamente 1 mg/ml a aproximadamente 2,5 mg/ml.

8. Una composición farmacéutica según la Reivindicación 5, en donde la concentración es entre aproximadamente 0,5 mg/ml a aproximadamente 3 mg/ml.

9. Una composición farmacéutica según cualquiera de las Reivindicaciones 1 a 3, en donde el antioxidante es L-cisteina.

10. Una composición farmacéutica según la Reivindicación 9, en donde la concentración de L-cisteina es entre aproximadamente 1 parte por millón a aproximadamente 8 mg/ml.

11. Una composición farmacéutica según la Reivindicación 10, en donde la concentración de L-cisteina es entre aproximadamente 1 mg/ml a aproximadamente 6 mg/ml.

12. Una composición farmacéutica según las Reivindicaciones 1 a 3, en donde el antioxidante es ácido tioglicólico.

13. Una composición farmacéutica según la Reivindicación 12, en donde la concentración de ácido tioglicólico es entre aproximadamente 1 parte por millón a aproximadamente 8 mg/ml.

14. Una composición farmacéutica según la Reivindicación 13, en donde la concentración de ácido tioglicólico es entre aproximadamente 0,1 (un décimo) mg/ml a aproximadamente 6 mg/ml.

JOSE LLOREDA CAMACHO & CO.

2-1032

31

INVESTOR IN PEOPLE

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

Signed [signature]

Dated 17 JAN 2001

Patents Form 1/77

Patents Act 1977
(Rule 16)

THE PATENT OFFICE
G
04 FEB 2000
LONDON

The Patent Office

35 32

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office
Cardiff Road
Newport
Gwent NP9 1RH

04 FEB 2000

1. Your reference

Z.1032

2. Patent application number
(The Patent Office will fill in this part)

0002691.4

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

LILLY FORSCHUNG GmbH,
ESSENER STRASSE 93,
D-22419 HAMBURG,
GERMANY

Patents ADP number *(if you know it)*

7828999001

If the applicant is a corporate body, give the country/state of its incorporation

GERMANY

4. Title of the invention

PHARMACEUTICAL COMPOSITION

5. Name of your agent *(if you have one)*

C. M. HUDSON

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

LILLY RESEARCH CENTRE,
ERL WOOD MANOR,
WINDLESHAM,
SURREY GU20 6PH

Patents ADP number *(if you know it)*

2303001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

YES

12

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	–
Description	6
Claim(s)	2
Abstract	1
Drawing(s)	–

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	1
Request for preliminary examination and search *(Patents Form 9/77)*	1
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature [signature] Date 4TH FEBRUARY 2000

12. Name and daytime telephone number of person to contact in the United Kingdom

MR. C. M. HUDSON (01276) 853443

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.

b) Write your answers in capital letters using black ink or you may type them.

c) If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.

d) If you have answered 'Yes' Patents Form 7/77 will need to be filed.

e) Once you have filled in the form you must remember to sign and date it.

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36 33

PHARMACEUTICAL COMPOSITION

The present invention relates to a stable, pharmaceutically elegant liquid composition comprising the known compound pemetrexed and an antioxidant selected from the group consisting of monothioglycerol, L-cysteine and thioglycolic acid and the salt forms thereof.

Certain folic acid antimetabolites are known to be antineoplastic agents. These compounds inhibit enzymatic conversion involving metabolic derivatives of folic acid. One such compound, described by United States Patent 5,473,071, is currently being developed for potential use as a pharmaceutical agent. This compound, known as pemetrexed, is most desirably formulated into a concentrated liquid for administration as an infusion dosage form. Premetrexed Disodium is the active ingredient in the anticancer drug ALIMTA now in clinical development by Eli Lilly and Company.

The formulation teachings of the US Patent 5,473,071 provide that the compounds claimed therein can be administered parenterally, and that isotonic saline solutions containing 20-100 mg/ml can be used for parenteral administration.

A ready to use stable solution that could be stored at room temperature is particularly desired for a pharmaceutical such as pemetrexed, wherein such ready to use formulation provides easier, safer handling, storage, and distribution. Further, a stable, ready to use formulation is more acceptable to the customer.

It was discovered that a simple, isotonic saline solution of pemetrexed is not pharmaceutically acceptable for commercial purposes due to degradation of the solution to form unacceptable related substances. It has now been discovered that pharmaceutically acceptable, concentrated, ready to use, liquid solutions of pemetrexed can prepared when the formulation includes certain antioxidants, including monothioglycerol, L-cysteine, and thioglycolic acid. Other antioxidants were studied; however, surprisingly, only these antioxidants provided the desired formulation characteristics described herein.

The claimed formulation exhibits acceptable stability, retains a pharmaceutically desirable appearance, maintains the desired enatiomeric stability,

and fulfils the health care provider's desire for a stable, ready to use liquid formulation. Additionally, the formulation provided herein, is suitable for parenteral dosage, can be delivered to the health care provider in a clear vial and can be stored at temperatures above 4 (four) Celcius in a highly concentrated state.

The present invention addresses the need for a pharmaceutically stable liquid pemetrexed formulation having both color stability and acceptable shelf life stability with regard to retaining the solution dosage form and avoiding unacceptable degradation to undesired related substances. Additionally, the claimed formulations can be diluted to the desired administration concentration by the health care provider. Finally, the formulations provided herein do not require the addition of any preservative, other than the antioxidant, in order to retain the desired concentration and stability.

The present invention particularly provides a pharmaceutical composition comprising:

a) pemetrexed;

b) at least one antioxidant selected from the group consisting of

i) monothioglycerol,

ii) L-cysteine,

iii) thioglycolic acid; and

c) a pharmaceutically acceptable excipient.

The three antioxidants are uniquely effective for the claimed formulation. Surprisingly, common antioxidants, such as sodium metabisulfite, ascorbic acid, sodium EDTA, monoethanolamine gentisate, sodium formaldehyde sulfoxylate, sodium bisulfite, did not provide the desired formulation characteristics.

An especially preferred antioxidant is monothioglycerol.

The concentration of monothioglycerol is most preferably from about 1 part per million to 8.0 mg/ml, which concentration may be optimized for a given formulation based on the oxygen concentration contacting the formulation. It may be preferred that the concentration of monothioglycerol is from about 0.6 mg/ml to about 6 mg/ml. More preferably, the concentration of monothioglycerol is from about 0.8

mg/ml to about 5.0 mg/ml. It is especially preferred that the concentration of monothioglycerol is at least 1.0 mg./ml. An especially desired concentration is from 1.40 mg/ml to about 3.0 mg/ml. A further desired concentration is from about 2 mg/ml to about 3 mg/ml. A further preferred concentration of monothioglycerol is from about 1.2 mg/ml to about 2.4 mg/ml.

In general, the antioxidant concentration of is most preferably from about 1 part per million to 8.0 mg/ml, which concentration may be optimized for a given formulation based on the oxygen concentration contacting the formulation. L-cysteine or thioglycerol are often most effective at a higher pH. It may be preferred that the concentration of antioxidant is from about 1.0 mg/ml to about 6 mg/ml. More preferably, the concentration of antioxidant is from about 0.8 mg/ml to about 5.0 mg/ml. It is especially preferred that the concentration of antioxidant is at least 1.0 mg./ml. An especially desired concentration for the antioxidant is from 1.40 mg/ml to about 3.0 mg/ml. A further desired concentration is from about 2 mg/ml to about 3 mg/ml. A further preferred concentration of antioxidant is from about 1.2 mg/ml to about 2.4 mg/ml.

Additionally, combinations of the three antioxidants, selected from monothioglycerol, L-cysteine and thioglycerol, may also be used in this invention.

The concentration of pemetrexed is preferably from about 20 to about 100 mg/ml. It is especially preferred that the pemetrexed concentration is from about 30 mg/ml to about 70 mg/ml. A further preferred embodiment is when the pemetrexed concentration is from about 35 mg/ml to about 50 mg/ml. A further preferred embodiment is a pemetrexed concentration of from 38 mg/ml to about 44 mg/ml. An especially desired concentration of pemetrexed is about 40 mg/ml.

As used herein, the term "pemetrexed" refers to the stable salts, acids and free base forms thereof. The term includes, for example, the free acid, the pharmaceutically acceptable alkali metal, alkaline earth metal, non-toxic metal, ammonium, and substituted ammonium salts, such as for example, the sodium, potassium, lithium, calcium, magnesium, aluminum, zinc, ammonium, trimethylammonium, triethylammonium, monoethanolammonium,

triethanolammonium, pyridinium, substituted pyridinium, and the like. The substituted ammonium salts are one especially preferred group of salts.

As used herein, the term "pharmaceutically acceptable excipient" means a pharmaceutically acceptable formulation carrier, solution or additive to enhance the formulation characteristics. Such additives are well known to the skilled artisan. While any pharmaceutically acceptable diluent is suitable, an especially preferred excipient for parenteral administration is saline solution. For example, sodium chloride, mannitol and the like.

The disodium salt of pemetrexed is particularly preferred for use in the present formulation.

The pH of the formulation is most preferably from about 5.5 to about 12. The formulation is more preferably from about pH 7 to about 11. It is especially desired that the pH of the formulation is from 8.0 to 9.0. It is further preferred that the pH is from about 8.4 to about 8.7 when the antioxidant is monothioglycerol. When the antioxidant is L-cysteine or thioglycolic acid or any salt form thereof, then the preferred pH is about 9.5.

It is generally preferred that the process for preparing the formulation includes the use of a purge of an inert gas. Such inert gases are for example, nitrogen, argon, and the like. The use of an isolator to maintain low oxygen conditions is desirable, but not required for the present formulation.

While any pharmaceutically acceptable stopper can be used to seal the vial containing the formulation, it is preferred to seal the vial with a stopper which is siliconized. A sterlized teflon coated stopper is desired for sealing the storage vial.

Most pharmaceutically acceptable liquid formulation vials or containers can be used to dispense the claimed formulation. It is desired that the containing vessel minimizes the concentration of oxygen that reaches the formulation. Thus, vials or ampules are especially desired vessels for the claimed formulation. A sealed vial is especially desired for commercial purposes in most countries.

The artisan will appreciate that the use of depyrogenated prewashed vials is desired for the storage of a sterile liquid formulation that is intended for parenteral use. The vial may be colored; however, a clear vial is acceptable for storage of the

formulation. Any pharmaceutically acceptable material may be used to make the formulation container; however, glass is an especially preferred container material. A glass vial is a preferred container. Other packaging materials for parenterals like plastic vials are preferred options as well. For example, Daikyo plastic vials may be useful.

It may be desirable to protect the bulk solution from light during the process of preparing the formulation; however, such protection is not required for the present formulation.

The resulting formulation can be sterlized using methods known to the artisan. Such sterilisation methods may include, for example, sterile filtration or heating. It is especially beneficial that the presently claimed formulation is stable during heat sterilization.

It is preferred that the headspace of the vial contains less than about 8 % v/v Oxygen. It is more preferred that the headspace of the vial contains from about 2% to about 5% Oxygen. It is especially preferred that the headspace contains from about 3% to about 5% Oxygen. The headspace of the vial can be adjusted to minimize the formulation contact with oxygen. It is generally desired that the headspace is not more than about 1/3 (one third) of the total volume of the container, with the fill taking at least about 2/3 (two thirds) of the total volume of the container. For example, it may be preferred that 5 ml of fill be used for a 7.5 ml vial. If a greater headspace ratio to fill is desired, then the concentration of the antioxidant may be adjusted as necessary.

The pharmaceutical formulation provided herein is suitable for both human clinical and veterinarian use for animals.

Pemetrexed can be prepared using the processes described in United States Patent 5,473,071, hereby incorporated by reference in its entirety. Compositions of pemetrexed are useful to treat cancer, as described in the 5,473,071 patent as well as in Seminars in Oncology, Vol. 26, No. 2, Supplement 6 (April 1999).

Monothioglycerol is commercially available from suppliers of fine chemicals which are well known to the artisan. To further clarify, Monothioglycerol is Chemical Abstracts number: 96-27-5.

Likewise, L-cysteine (CAS: 52-90-4), L-cysteine hydrochloride monohydrate (CAS: 7048-04-6), L-cycsteine hydrochloride monohydrate anhydrous (CAS: 52-89-1) and thioglycolic acid (CAS:68-11-1) are readily obtained from suppliers of fine chemicals.

Description of Preferred Embodiments.

The Present invention is seen more fully by the examples given below.

Example 1

Pemetrexed, was prepared as a 40 mg/ml in water. Monothioglyceraol was prepared as a 2.4 mg/ml solution using water for injection. The pH of the monothioglycerol solution was adjusted to 8.5 using sodium hydroxide.

The bulk solution was protected from light. The solution was purged with nitrogen for twenty minutes and then sterile filtered. The formulation was dispensed into prewashed, depyrogenated vials and then stoppered with a prewashed, presterilized teflon coated stopper. Caps were attached using a crimper. The sterile filtration and dispensing steps were conducted using a nitrogen isolator (5% v/v Oxygen).

The solution filled vials were heat sterlized.

Example 2

A pharmaceutical composition was prepared substantially as described herein by Example 1, except that the antioxidant was 0.03% L-Cysteine and the pemetrexed concentration was four percent (4%).

Example 3

A pharmaceutical composition was prepared substantially as described herein by Example 1, except that the antioxidant was 0.03% Thioglycolate and the pemetrexed concentration was four percent (4%).

We Claim:

1. A pharmaceutical composition comprising:

a) pemetrexed;

b) at least one antioxidant selected from the group consisting of:

c) monothioglycerol,

ii) L-cysteine, and

iii) thioglycolic acid; and

c) a pharmaceutically acceptable excipient.

2. A pharmaceutical composition as claimed by Claim 1 wherein the composition is a liquid formulation suitable for parenteral administration.

3. A pharmaceutical composition as claimed by any one of Claims 1 to 2 wherein premetrexed is the disodium salt.

4. A pharmaceutical composition as claimed by any one of Claims 1 to 3 wherein the antioxidant is monothioglycerol.

5. A pharmaceutical composition of Claims 1 to 4 wherein the monothioglycerol concentration is from about 1 (one) part per million to about 8 (eight) milligrams per milliliter.

6. A pharmaceutical composition of Claim 5 wherein the monothioglycerol concentration is from about 1 (one) mg/ml to about 6 (six) mg/ml.

7. A pharmaceutical composition of Claim 6 wherein the monothioglycerol concentration is from about 1 (one) mg/ml to about 2.5 (two and one half) mg/ml.

8. A pharmaceutical composition of Claim 5 wherein the concentration is from about 0.5 (one half) mg/ml to about 3 (three) mg/ml.

9. A pharmaceutical composition as claimed by any one of Claims 1 to 3 wherein the antioxidant is L-cysteine.

10. A pharmaceutical composition of Claim 9 wherein the L-cysteine concentration is from about 1 (one) part per million to about 8 (eight) mg/ml.

11. A pharmaceutical composition of Claim 10 wherein the L-cysteine concentration is from about 1 (one) mg/ml to about 6 (six) mg/ml.

12. A pharmaceutical composition of Claims 1 to 3 wherein the antioxidant is thioglycolic acid.

13. A pharmaceutical composition of Claim 12 wherein the thioglycolic acid concentration is from about 1 (one) part per million to about 8 (eight) mg/ml.

14. A pharmaceutical composition of Claim 13 wherein the thioglycolic acid concentration is from about 0.1 (one-tenth) mg/ml to about 6 (six) mg/ml.

Abstract

The present invention provides a pharmaceutical composition comprising pemetrexed; at least one antioxidant selected from the group consisting of monothioglycerol, L-cysteine, and thioglycolic acid; and a pharmaceutically acceptable excipient. The pharmaceutical formulation is suitable for liquid parenteral administration.

Eli Lilly
21032
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OFICINA DE PATENTES

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El suscrito, un funcionario debidamente autorizado conforme a los Artículos 74(1) y (4) de la Ley de Desreglamentación y Contratación de 1994 para firmar y expedir certificados en nombre del Contralor General, certifico que la copia adjunta es una copia correcta de los documentos archivados originalmente con respecto a la solicitud de patente que allí se identifica.

De acuerdo con las Reglamentaciones de Patentes de 1982 (Re-registro de Compañías), si una compañía nombrada en este certificado y en los documentos adjuntos se ha vuelto a registrar según la Ley de Compañías de 1980 con el mismo nombre con el que fue registrada inmediatamente antes del re-registro, salvo la sustitución o inclusión como la última parte del nombre de las palabras "sociedad anónima" o su equivalente en galés, las referencias al nombre de la compañía y sus documentos adjuntos serán tratadas como referencias al nombre con el cual fue re-registrada.

De acuerdo con las reglas, las palabras "sociedad anónima" (o en inglés *public limited company)* pueden ser reemplazadas por las letras p.l.c, plc. P.L.C ó PLC.

El re-registro bajo la Ley de Compañías no constituye una nueva entidad legal sino simplemente somete a la compañía a ciertas normas de ley adicionales.

(FIRMA) R. MAHONEY FECHA: 17 de enero de 2001
(SELLO DE LACRE)

María Mercedes Uncaechea
Reg. No. 10437 [illegible]

Maria Uncaechea

OFICINA DE PATENTES

SOLICITUD DE PATENTE

1. Su referencia: **Z. 1032-A**

2. Solicitud No. **0019599.0** 09 de agosto de 2000

3. Nombre completo y código postal de cada solicitante:

Dirección: LILLY FORSCHUNG GmbH.
ESSENER STRASSE 93,
D-22419 HAMBURGO
ALEMANIA

ADP 07683238002

Si el solicitante es una entidad, indique el pais/estado de constitución:
ALEMANIA

TITULO DEL INVENTO:

COMPOSICIÓN FARMACÉUTICA

5. NOMBRE DE SU AGENTE:

Nombre del Agente: C. M. HUDSON

Dirección para notificaciones: LILLY RESEARCH CENTRE
ERL WOOD MANOR
WINDLESHAM
SURREY GU20 6PH

NO. ADP Patentes 2303001

María Mercedes [illegible]
Traductora Jurament[illegible]

6. Si declara prioridad de una o más patentes anteriores, indique el pais y la fecha de radicación de cada una de ellas: N/A

7. N/A

8. SI

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9. Número de hojas radicadas (En inglés). Descripción: 7 Reivindicaciones: 3

Resumen : 1 Dibujos: 0

10. Solicitud de examen preliminar y búsqueda :

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11. Solicitamos se nos adjudique una patente con base en esta solicitud.

C.M. HUDSON, 8 de agosto de 2000

12. Nombre y teléfono del contacto en el Reino Unido Nombre y teléfono del contacto en el Reino Unido (FIRMA) C.M. HUDSON (01276) 853443

María Mercedes [illegible] Traductora Juramentada

COMPOSICIÓN FARMACÉUTICA

REIVINDICACIONES:

1. Una composición farmacéutica que comprende:

a) un pemetrexo

b) al menos un antioxidante seleccionado del grupo compuesto por:

i) monotioglicerol

ii) L-cisteína, y

iii) ácido tioblicólico; y

c) un excipiente farmacéuticamente aceptable

2. Una composición farmacéutica según la Reivindicación 1, en donde la composición es una formulación liquida adecuada para administración parenteral.

3. Una composición farmacéutica según cualquiera de las Reivindicaciones 1 a 2, en donde el premetrexo es la sal disódica.

4. Una composición farmacéutica según cualquiera de las reivindicaciones 1 a 3, en donde el antioxidante es monotioglicerol

5. Una composición farmacéutica según cualquiera de las Reivindicaciones 1 a 4, en donde la concentración de monotioglicerol es

entre aproximadamente 1 parte por millón a aproximadamente 8 miligramos por milímetro.

6. Una composición farmacéutica según la Reivindicación 5, en donde la concentración de monotioglicerol es entre aproximadamente 1 mg/ml a aproximadamente 6 mg/ml.

7. Una composición farmacéutica según la Reivindicación 6, en donde la concentración de monotioglicerol es entre aproximadamente 1 mg/ml a aproximadamente 2,5 mg/ml.

8. Una composición farmacéutica según la Reivindicación 5, en donde la concentración es entre aproximadamente 0,5 mg/ml a aproximadamente 3 mg/ml.

9. Una composición farmacéutica según cualquiera de las Reivindicaciones 1 a 3, en donde el antioxidante es L-cisteina.

10. Una composición farmacéutica según la Reivindicación 9, en donde la concentración de L-cisteina es entre aproximadamente 1 parte por millón a aproximadamente 8 mg/ml.

11. Una composición farmacéutica según la Reivindicación 10, en donde la concentración de L-cisteina es entre aproximadamente 1 mg/ml a aproximadamente 6 mg/ml.

12. Una composición farmacéutica según las Reivindicaciones 1 a 3, en donde el antioxidante es ácido tioglicólico.

13. Una composición farmacéutica según la Reivindicación 12, en donde la concentración de ácido tioglicólico es entre aproximadamente 1 parte por millón a aproximadamente 8 mg/ml.

14. Una composición farmacéutica según la Reivindicación 13, en donde la concentración de ácido tioglicólico es entre aproximadamente 0,1 (un décimo) mg/ml a aproximadamente 6 mg/ml.

15. Una composición farmacéutica según la Reivindicación 4, en donde la concentración de monotiogliceról es entre aproximadamente 0,1 (un décimo) mg/ml a aproximadamente 10 mg/ml.

16. Una composición farmacéutica según la Reivindicación 15 en donde la concentración de monotiogliceról es entre aproximadamente 0,1 (un décimo) mg/ml a aproximadamente 6 mg/ml.

17. Una composición farmacéutica según la Reivindicación 9 en donde la L-cisteina es entre aproximadamente 0,1 (un décimo) mg/ml a aproximadamente 10 mg/ml.

18. Una composición farmacéutica según la Reivindicación 17 en donde la L-cisteina es entre aproximadamente 0,1 (un décimo) mg/ml a aproximadamente 6 mg/ml.

19. Una composición farmacéutica según la Reivindicación 12 en donde el ácido tioglicólico es entre aproximadamente 0,1 (un décimo) mg/ml a aproximadamente 10 mg/ml.

20. Una composición farmacéutica según la Reivindicación 19 en donde el ácido tioglicólico es entre aproximadamente 0,1 (un décimo) mg/ml a aproximadamente 6 mg/ml.

INVESTOR IN PEOPLE

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

Signed R. Mahoney

Dated 17 JAN 2001

Patents Form 1/77

1. ...ats Act 1977
(Rule 16)

THE PATENT OFFICE
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- 9 AUG 2000
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Patent Office

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P01/7700 0.00-0019599.0

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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference — Z.1032A

2. Patent application number *(The Patent Office will fill in this part)* — 09 AUG 2000 — 0019599.0

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

LILLY FORSCHUNG GmbH,
ESSENER STRASSE 93,
D-22419 HAMBURG,
GERMANY

Patents ADP number *(if you know it)* ...

If the applicant is a corporate body, give the country/state of its incorporation — GERMANY

4. Title of the invention — PHARMACEUTICAL COMPOSITION

5. Name of your agent *(if you have one)* — C. M. HUDSON

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

LILLY RESEARCH CENTRE,
ERL WOOD MANOR,
WINDLESHAM,
SURREY GU20 6PH

Patents ADP number *(if you know it)* — 2303001 ✓

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

YES

26

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	–
Description	7
Claim(s)	3
Abstract	1
Drawing(s)	–

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	1
Request for preliminary examination and search *(Patents Form 9/77)*	1
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature [signature] Date 8TH AUGUST 2000

12. Name and daytime telephone number of person to contact in the United Kingdom

MR. C. M. HUDSON 01276 853443

Warning

*After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 19**. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.*

Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.

b) Write your answers in capital letters using black ink or you may type them.

c) If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.

d) If you have answered 'Yes' Patents Form 7/77 will need to be filed.

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f) For details of the fee and ways to pay please contact the Patent Office.

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47

DUPLICATE

PHARMACEUTICAL COMPOSITION

The present invention relates to a liquid composition comprising the known compound pemetrexed, in particular, the present invention relates to a liquid composition comprising pemetrexed and an antioxidant; which liquid composition is stable and pharmaceutically elegant.

Certain folic acid antimetabolites are known to be antineoplastic agents. These compounds inhibit enzymatic conversion involving metabolic derivatives of folic acid. One such compound, described by United States Patent 5,473,071, is currently being developed for potential use as a pharmaceutical agent. This compound, known as "pemetrexed", is most desirably formulated into a concentrated liquid for administration as an infusion dosage form. Pemetrexed Disodium is the active ingredient in the anticancer drug ALIMTA now in clinical development by Eli Lilly and Company.

The formulation teachings of the US Patent 5,473,071 provide that the compounds claimed therein can be administered parenterally, and that isotonic saline solutions containing 20-100 mg/ml can be used for parenteral administration.

A ready to use stable solution that could be stored at room temperature is particularly desired for a pharmaceutical such as pemetrexed, wherein such ready to use formulation provides easier, safer handling, storage, and distribution. Further, a stable, ready to use formulation is more acceptable to the customer.

It was discovered that a simple, isotonic saline solution of pemetrexed is not pharmaceutically acceptable for commercial purposes due to degradation of the solution to form unacceptable related substances. It has now been discovered that pharmaceutically acceptable, concentrated, ready to use, liquid solutions of pemetrexed may be prepared when the formulation includes certain antioxidants, including monothioglycerol, L-cysteine, and thioglycolic acid. Other antioxidants were studied; however, surprisingly, of the antioxidants studied, only these provided the desired formulation characteristics described herein.

The claimed formulation exhibits acceptable stability, retains a pharmaceutically desirable appearance, maintains the desired enatiomeric stability, and fulfils the health care provider's desire for a stable, ready to use liquid formulation. Additionally, the formulation provided herein, is suitable for parenteral dosage, can be delivered to the health care provider in a clear vial and can be stored at temperatures above 4 (four) Celcius in a highly concentrated state.

The present invention addresses the need for a pharmaceutically stable liquid pemetrexed formulation having both color stability and acceptable shelf life stability with regard to retaining the solution dosage form and avoiding unacceptable degradation to undesired related substances. Additionally, the claimed formulations can be diluted to the desired administration concentration by the health care provider. Finally, the formulations provided herein do not require the addition of any preservative, other than the antioxidant, in order to retain the desired concentration and stability.

The present invention particularly provides a pharmaceutical composition comprising:

a) pemetrexed;

b) at least one antioxidant selected from the group consisting of

i) monothioglycerol,

ii) L-cysteine,

iii) thioglycolic acid; and

c) a pharmaceutically acceptable excipient.

The three antioxidants are uniquely effective for the claimed formulation. Surprisingly, common antioxidants, such as sodium metabisulfite, ascorbic acid, sodium EDTA, monoethanolamine gentisate, sodium formaldehyde sulfoxylate, sodium bisulfite, did not provide the desired formulation characteristics.

An especially preferred antioxidant is monothioglycerol.

The concentration of monothioglycerol is most preferably from about 1 part per million to 8.0 mg/ml, which concentration may be optimized for a given formulation based on the oxygen concentration contacting the formulation. The

concentration of monothioglycerol may preferably be at least 0.6 mg/ml, more preferably at least 0.8 mg/ml, especially preferably is at least 1.0 mg/ml. The concentration of monothioglycerol is preferably up to 6 mg/ml, more preferably up to 5 mg/ml, and most preferably is up to 3 mg/ml.

It may be preferred that the concentration of monothioglycerol is from about 0.6 mg/ml to about 6 mg/ml. More preferably, the concentration of monothioglycerol is from about 0.8 mg/ml to about 5.0 mg/ml. It is especially preferred that the concentration of monothioglycerol is at least 1.0 mg./ml. An especially desired concentration is from 1.40 mg/ml to about 3.0 mg/ml. A further desired concentration is from about 2 mg/ml to about 3 mg/ml. A further preferred concentration of monothioglycerol is from about 1.2 mg/ml to about 2.4 mg/ml.

In general, the concentration of monothioglycerol, L-cysteine or Thioglycolic acid is most preferably from about 1 part per million to 8.0 mg/ml, which concentration may be optimized for a given formulation based on the oxygen concentration contacting the formulation. L-cysteine or thioglycerol are often most effective at a higher pH. It may be preferred that the concentration of monothioglycerol, L-cysteine or Thioglycolic acid is from about 1.0 mg/ml to about 6 mg/ml. More preferably, the concentration of monothioglycerol, L-cysteine or Thioglycolic acid is from about 0.8 mg/ml to about 5.0 mg/ml. It is especially preferred that the concentration of monothioglycerol, L-cysteine or Thioglycolic acid is at least 1.0 mg./ml. An especially desired concentration for monothioglycerol, L-cysteine or Thioglycolic acid is from 1.40 mg/ml to about 3.0 mg/ml. A further desired concentration is from about 2 mg/ml to about 3 mg/ml. A further preferred concentration of monothioglycerol, L-cysteine or Thioglycolic acid is from about 1.2 mg/ml to about 2.4 mg/ml. It is preferred to have a concentration of from about 0.1 (one tenth) mg/ml to 7 mg/ml. When the antioxidant is monothioglycerol or L-cycsteine, the preferred concentration range is from about 0.1 (one tenth)mg/ml to about 10.0 mg/ml.

The concentration of L-cysteine is preferably greater than 0.1 (one tenth) mg/ml, more preferably greater than 0.5 (one half) mg/ml and most preferably greater than 1 (one) mg/ml.

The concentration of L-cysteine is preferably less than 10 (ten) mg/ml, more preferably less than 8 (eight) mg/ml, and most preferably less than 6 (six) mg/ml.

The concentration of thioglycolic acid is preferably greater than 0.1 (one-tenth) mg/ml, more preferably greater than 0.5 (one-half) mg/ml and most preferably greater than 1 (one) mg/ml.

The concentration of thioglycolic acid is preferably less than 10 (ten) mg/ml, more preferably less than 8 (eight) mg/ml, and most preferably less than 6 (six) mg/ml.

Additionally, combinations of the three antioxidants, selected from monothioglycerol, L-cysteine and thioglycerol, may also be used in this invention.

The concentration of pemetrexed is preferably from about 20 to about 100 mg/ml. It is especially preferred that the pemetrexed concentration is from about 30 mg/ml to about 70 mg/ml. A further preferred embodiment is when the pemetrexed concentration is from about 35 mg/ml to about 50 mg/ml. A further preferred embodiment is a pemetrexed concentration of from 38 mg/ml to about 44 mg/ml. An especially desired concentration of pemetrexed is about 40 mg/ml.

As used herein, the term "pemetrexed" refers to the stable salts, acids and free base forms thereof. The term includes, for example, the free acid, the pharmaceutically acceptable alkali metal, alkaline earth metal, non-toxic metal, ammonium, and substituted ammonium salts, such as for example, the sodium, potassium, lithium, calcium, magnesium, aluminum, zinc, ammonium, trimethylammonium, triethylammonium, monoethanolammonium, triethanolammonium, pyridinium, substituted pyridinium, and the like. The substituted ammonium salts are one especially preferred group of salts.

As used herein, the term "pharmaceutically acceptable excipient" means a pharmaceutically acceptable formulation carrier, solution or additive to enhance the formulation characteristics. Such additives are well known to the skilled artisan. While any pharmaceutically acceptable diluent is suitable, an especially preferred excipient for parenteral administration is saline solution. For example, sodium chloride, mannitol and the like.

The disodium salt of pemetrexed is particularly preferred for use in the present formulation.

The pH of the formulation is most preferably from about 5.5 to about 12. The formulation is more preferably from about pH 7 to about 11. It is especially desired that the pH of the formulation is from 8.0 to 9.0. It is further preferred that the pH is from about 8 to about 9 when the antioxidant is monothioglycerol. When the antioxidant is L-cysteine or thioglycolic acid or any salt form thereof, then the preferred pH is about 8 to about 10. The artisan will appreciate that combinations of these antioxidants can provide new preferred pH ranges. Standard modifications of the composition can provide compositions of various pH within the contemplation of this invention.

It is generally preferred that the process for preparing the formulation includes the use of a purge of an inert gas. Such inert gases are for example, nitrogen, argon, and the like. The use of an isolator to maintain low oxygen conditions is desirable, but not required for storage of the present formulation.

While any pharmaceutically acceptable stopper may be used to seal the vial containing the formulation, it is preferred to seal the vial with a stopper which is siliconized. A sterlized teflon coated stopper is desired for sealing the storage vial.

Most pharmaceutically acceptable liquid formulation vials or containers can be used to dispense the claimed formulation. It is desired that the containing vessel minimizes the concentration of oxygen that reaches the formulation. Thus, vials or ampules are especially desired vessels for the claimed formulation. A sealed vial is especially desired for commercial purposes in most countries.

The artisan will appreciate that the use of depyrogenated prewashed vials is desired for the storage of a sterile liquid formulation that is intended for parenteral use. The vial may be colored; however, a clear vial is acceptable for storage of the formulation. Any pharmaceutically acceptable material may be used to make the formulation container; however, glass is an especially preferred container material. A glass vial is a preferred container. Other packaging materials for parenterals like plastic vials are preferred options as well. For example, plastic vials may be useful.

It may be desirable to protect the bulk solution from light during the process of preparing the formulation; however, such protection is not required for the present formulation.

The resulting formulation can be sterlized using methods known to the artisan. Such sterilisation methods may include, for example, sterile filtration or heating. It is especially beneficial that the presently claimed formulation is stable during heat sterilization.

It is preferred that the headspace of the vial contains less than about 8% (eight percent) v/v Oxygen; however, the headspace of the vial may contain more than 8% oxygen if other conditions of the formulation are appropriately adjusted. It is more preferred that the headspace of the vial contains from about 2% to about 5% Oxygen. It is especially preferred that the headspace contains from about 3% to about 5% Oxygen. It is further preferred that the headspace contains less than about one (1) ppm oxygen. Also, preferred is when the headspace oxygen content is less than about 0.1% (one tenth percent) v/v oxygen. It is also a preferred condition that the headspace of the vial is less than about 1% (one percent) oxygen.

The headspace of the vial can be adjusted to minimize the formulation contact with oxygen. It is generally desired that the headspace is not more than about 1/3 (one third) of the total volume of the container, with the fill taking at least about 2/3 (two thirds) of the total volume of the container. For example, it may be preferred that 5 ml of fill be used for a 7.5 ml vial. If a greater headspace ratio to fill is desired, then the concentration of the antioxidant may be adjusted as necessary.

The pharmaceutical formulation provided herein is suitable for both human clinical use and veterinarian use for animals.

Pemetrexed can be prepared using the processes described in United States Patent 5,473,071, hereby incorporated by reference in its entirety. Compositions of pemetrexed are useful to treat cancer, as described in the 5,473,071 patent as well as in Seminars in Oncology, Vol. 26, No. 2, Supplement 6 (April 1999).

Monothioglycerol is commercially available from suppliers of fine chemicals which are well known to the artisan. To further clarify, Monothioglycerol is Chemical Abstracts number: 96-27-5.

Likewise, L-cysteine (CAS: 52-90-4), L-cysteine hydrochloride monohydrate (CAS: 7048-04-6), L-cycsteine hydrochloride monohydrate anhydrous (CAS: 52-89-1) and thioglycolic acid (CAS:68-11-1) are readily obtained from suppliers of fine chemicals.

Description of Preferred Embodiments.

The Present invention is seen more fully by the examples given below.

Example 1

Pemetrexed, was prepared as a 40 mg/ml solution in water. Monothioglycerol was prepared as a 2.4 mg/ml solution using water for injection. The pH of the monothioglycerol solution was adjusted to 8.5 using sodium hydroxide.

The bulk solution was protected from light. The solution was purged with nitrogen for twenty minutes and then sterile filtered. The formulation was dispensed into prewashed, depyrogenated vials and then stoppered with a prewashed, presterilized teflon coated stopper. Caps were attached using a crimper. The sterile filtration and dispensing steps were conducted using a nitrogen isolator (5% v/v Oxygen).

The solution filled vials were heat sterlized.

Example 2

A pharmaceutical composition was prepared substantially as described herein by Example 1, except that the antioxidant was 0.03% L-Cysteine and the pemetrexed concentration was four percent (4%).

Example 3

A pharmaceutical composition was prepared substantially as described herein by Example 1, except that the antioxidant was 0.03% Thioglycolate and the pemetrexed concentration was four percent (4%).

We Claim:

1. A pharmaceutical composition comprising:

a) pemetrexed;

b) at least one antioxidant selected from the group consisting of:

c) monothioglycerol,

ii) L-cysteine, and

iii) thioglycolic acid; and

c) a pharmaceutically acceptable excipient.

2. A pharmaceutical composition as claimed by Claim 1 wherein the composition is a liquid formulation suitable for parenteral administration.

3. A pharmaceutical composition as claimed by any one of Claims 1 and 2 wherein pemetrexed is the disodium salt.

4. A pharmaceutical composition as claimed by any one of Claims 1 to 3 wherein the antioxidant is monothioglycerol.

5. A pharmaceutical composition as claimed in any one of Claims 1 to 4 wherein the monothioglycerol concentration is from about 1 (one) part per million to about 8 (eight) milligrams per milliliter.

6. A pharmaceutical composition of Claim 5 wherein the monothioglycerol concentration is from about 1 (one) mg/ml to about 6 (six) mg/ml.

7. A pharmaceutical composition of Claim 6 wherein the monothioglycerol concentration is from about 1 (one) mg/ml to about 2.5 (two and one half) mg/ml.

8. A pharmaceutical composition of Claim 4 wherein the monothioglycerol concentration is from about 0.5 (one half) mg/ml to about 3 (three) mg/ml.

9. A pharmaceutical composition as claimed by any one of Claims 1 to 3 wherein the antioxidant is L-cysteine.

10. A pharmaceutical composition of Claim 9 wherein the L-cysteine concentration is from about 1 (one) part per million to about 8 (eight) mg/ml.

11. A pharmaceutical composition of Claim 10 wherein the L-cysteine concentration is from about 1 (one) mg/ml to about 6 (six) mg/ml.

12. A pharmaceutical composition of Claims 1 to 3 wherein the antioxidant is thioglycolic acid.

13. A pharmaceutical composition of Claim 12 wherein the thioglycolic acid concentration is from about 1 (one) part per million to about 8 (eight) mg/ml.

14. A pharmaceutical composition of Claim 13 wherein the thioglycolic acid concentration is from about 0.1 (one-tenth) mg/ml to about 6 (six) mg/ml.

15. A pharmaceutical composition of Claim 4 wherein the monothioglycerol concentration is from about 0.1 (one tenth) mg/ml to about 10 (ten) mg/ml.

16. A pharmaceutical composition of Claim 15 wherein the monothioglycerol concentration is from about 0.1 (one tenth) mg/ml to about 6 (six) mg/ml.

17. A pharmaceutical composition of Claim 9 wherein the L-cysteine is from about 0.1 (one tenth) mg/ml to about 10 (ten) mg/ml.

18. A pharmaceutical composition of Claim 17 wherein the L-cysteine is from about 0.1 (one tenth) mg/ml to about 6 (six) mg/ml.

19. A pharmaceutical composition of Claim 12 wherein the thioglycolic acid is from about 0.1 (one tenth) mg/ml to about 10 (ten) mg/ml.

20. A pharmaceutical composition of Claim 19 wherein the thioglycolic acid is from about 0.1 (one tenth) mg/ml to about 6 (six) mg/ml.

Abstract

The present invention provides a pharmaceutical composition comprising pemetrexed; at least one antioxidant selected from the group consisting of monothioglycerol, L-cysteine, and thioglycolic acid; and a pharmaceutically acceptable excipient. The pharmaceutical formulation is suitable for liquid parenteral administration.

Eli Lilly
53
Z-1032

TRADUCCION OFICIAL No. 485

LEGALIZACION DE UN DOCUMENTO PRESENTADO SIMULTANEAMENTE EN INGLES Y ESPAÑOL. TRASPASO INVENCION ***COMPOSICION FARMACEUTICA*** *A FAVOR DE* ***ELI LILLY AND COMPANY.***

TRASPASO **COLOMBIA**

CASO: Z-1032

INVENCION: **COMPOSICION FARMACEUTICA**

Firmado: **Bernd Ulrich Riebesehl**

Firmado: **Jens Kemken**

[illegible]

Dr. ERWIN TIEDAU
Dr. PETER SIEVEKING
Dr. ARNOLD SIEVEKING
Dr. PAUL-JOACHIM V. WISSEL
Dr. AXEL PFEIFER
Dr. TIL BRÄUTIGAM

NOTARIO

Bergstrasse 11, 20095 Hamburg

Reg. Not. 2001 No. 979

La presente és para certificar que ante mi, Dr. Til Bräutigam, Notario en y para la Ciudad Libre y Hanseática de Hamburgo, Alemania, debidamente admitido y juramentado, comparecieron

Dr. Bernd Ulrich Riebesehl
Identificado con la tarjeta de identidad No. 1340003872
Residente en Ernst-Mittelbach-Ring 15, 22455 Hamburg
Y
Sr. Jens Kemken
Identificado con tarjeta de identidad No. 2002823795
Residente en Thüreystrasse 11, 22455 Hamburgo
Y reconocieron las firmas que aparecen en el documento anterior como un acto suyo libre y voluntario.

En fe de lo cual mi firma y sello.

Hamburgo, Febrero 2, 2001.
Firmado: (firma ilegible)
Sello del Notario de Hamburgo, Dr. Til Bräutigam

TRADUCCION OFICIAL No. 8239
de un documento escrito en Alemán, el cual para su identificación se sella con el sello de la traductora, lo mismo que la presente.-

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Traducción de las legalizaciones en alemán que se encuentra a continuación de un documento por el cual se ceden a ELI LILLY AND COMPANY, domiciliada en Indiana, USA, todos los derechos inherentes a la invención COMPOSICION FARMACEUTICA. Hay 2 firmas ilegibles de los señores Bernd Ulrich Riebesehl y Jens Kemken.

APOSTILLA
(Convención de La Haya)

1. País: República Federal de Alemania
   Este documento público
2. Ha sido firmado por el Dr. Til Bräutigam
3. Actuando en calidad de notario
4. Lleva el sello del

Notario Til Bräutigam

Certificado

5. en Hamburgo 6. El 5 de marzo 2001
7. por la Presidente del Tribunal Regional
8. bajo el No 9101 E/I - 325/2001
9. Sello 10. Firma
El Presidente del Fdo.: firma ilegible
Tribunal Regional de Hamburgo Görres-Ohde

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

Bogotá, 28 de marzo 2001.

LUZ ARRIAGA DE HERBER
TRADUCTORA E INTERPRETE OFICIAL
Resolución No.599 Minjusticia

MINISTERIO DE RELACIONES EXTERIORES

Juz

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Quiaga

CUYA FIRMA APARECE EN EL DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS

CID SE ASUME RESPONSABILIDAD DEL TEXTO

2001 MAR 29 P 4:10

JEFE DE LEGALIZACIONES SANTAFE DE BOGOTA D.C.

35

Eli Lilly And Company

COLOMBIA
CASE: Z-1032 56

ASSIGNMENT

The undersigned

Bernd Ulrich Riebesehl and Jens Kemken

domiciled in

Ernst-Mittelbach-Ring 15, 22455 Hamburg, Germany, and Thuereystr. 11, 22419 Hamburg, Germany (respectively)

hereby state under oath to be the sole and true inventor(s) of

PHARMACEUTICAL COMPOSITION

states as well that he/they assign, without reservations or limitation, in favor of

ELI LILLY AND COMPANY

a corporation organized and existing under the laws of the State of Indiana, United States of America

domiciled in Lilly Corporate Center Indianapolis, Indiana 46285 United States of America

All rights inherent to said invention, and that the above mentioned corporation hereby to apply, in its name, for the corresponding patent in the Republic of Colombia.

Bernd Ulrich Riebesehl

Jens Kemken

TRASPASO

abajo firmado

Bernd Ulrich Riebesehl and Jens Kemken

domiciliado en

Ernst-Mittelbach-Ring 15, 22455 Hamburg, Alemania, y Thuereystr. 11, 22419 Hamburgo, Alemania.

decia bajo juramnto ser único y verdadero inventor de

COMPOSICION FARMACEUTICA

Declar asimismo que ced y transf sin reserva ni limitacion, a favor de la sociedad

ELI LILLY AND COMPANY

organizada y existente de conformidad con las leyes del Estado de Indiana, Estados Unidos de America.

domiciliada en Lilly Corporate Center Indianapolis, Indiana 46285 Estados Unidos de America

todos los dorechos inherentes a dicha invención y que la citada sociedad queda facultada para solicitar en su nombre la patente correspondiente en la República de Colombia.

57

DR. ERWIN TIEDAU
DR. PETER SIEVEKING
DR. ARNOLD SIEVEKING
DR. PAUL-JOACHIM V. WISSEL
DR. AXEL PFEIFER
DR. TIL BRÄUTIGAM
NOTARE
Bergstraße 11, 20095 Hamburg
Tel.Sa.Nr. (040) 30 20 060
Telefax (040) 30 20 06 35

Not.Reg.2001 No. 979

This is to certify that before me,Dr.Til Bräutigam, a notary in and for the Free and Hanseatic City of Hamburg,Germany,duly admitted and sworn in,there appeared
Dr.Bernd Ulrich Riebesehl
identified by identity card no. 134ooo3872
residing at Ernst-Mittelbach-Ring 15,22455 Hamburg
and
Mr. Jens Kemken
identified by identity card no. 2oo2823795
residing at Thüreystrasse 11,22455 Hamburg
and acknowledged their foregoing signatures as their free act and deed.
Witness my hand and seal.
Hamburg,February 2,2oo1

GT 58

Apostille

(Convention de La Haye du 5 octobre 1961)

1. Land: Bundesrepublik Deutschland

   Diese öffentliche Urkunde

2. ist unterschrieben von Dr. Til Bräutigam

3. in der Eigenschaft als Notar

4. sie ist versehen mit dem Siegel/Stempel) des

   Notars Dr. Til Bräutigam

   Bestätigt

5. in Hamburg 6. am 5. März 2001

7. durch die Präsidentin des Landgerichts

8. unter Nr. 9101 E/I -325/2001

9. Siegel/Stempel 10. Unterschrift:

Landgericht Hamburg 126 Hamburg

Görres-Ohde

68 Eli Lilly And company
1
59 01.007.346

TRADUCCION OFICIAL No. 8332
de un documento escrito en Alemán, el cual para su identificación se sella con el sello de la traductora, lo mismo que la presente.-

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Traducción de la apostilla en alemán que se encuentra a continuación de un Traspaso de Patente de la LILLY FORSCHUNG GmbH, domiciliada en Hamburgo, Alemania, a ELI LILLY AND COMPANY, domiciliada en Indianapolis, Indiana 46285 USA, de fecha 1 de marzo 2001.

APOSTILLA

(Convención de La Haya del 5 de octubre 1961)

1. País: República Federal de Alemania
   Este documento público
2. Ha sido firmado por Ulrike Glück
3. Actuando en calidad de notaria suplente oficialmente designada
4. Lleva el sello del **notario Dr. Paul-Joachim von Wissel**

Certificado

5. en Hamburgo — 6. el 6 de marzo 2001
7. por la Presidente del Tribunal Regional
8. bajo el No 9101 E/I - 335/2001
9. Sello — 10. Firma

Tribunal Regional de Hamburgo — firma ilegible
Görres-Ohde

ES TRADUCCION FIEL Y COMPLETA, de la cual se deja copia en los archivos de estas oficinas para su confrontación.
Bogotá, 30 de abril 2001.

LUZ ARRIAGA DE HERBER
TRADUCTORA E INTERPRETE OFICIAL
Resolución No. [illegible]

MINISTERIO DE RELACIONES EXTERIORES

131315

CUYA FIRMA APARECE EN EL DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS

NO SE ASUME RESPONSABILIDAD DEL TEXTO

2001 MAY -3 P 2:55

JEFE DE LEGALIZACIONES SANTAFE DE BOGOTA D.C.

60

TRADUCCION OFICIAL NO. 8251

De un documento escrito en inglés.

= = = = = =

COLOMBIA

Nuestro Caso: Z-1032

EXPEDIENTE 01-007.346

TRASPASO DE PATENTE

La suscrita, LILLY FORSCHUNG GmbH, una sociedad domiciliada en Essener Strasse 93,22419 Hamburgo, Alemania, dueña de las Solicitudes de la Gran Bretaña No. 0002691.4 y 0019599.0, presentadas en Febrero 4 de 2000 y Agosto 9 de 2000 (respectivamente) por el presente transfiere y traspasa en su totalidad el derecho a presentar una solicitud de patente correspondiente a dichas solicitudes de la Gran Bretaña en Colombia a ELI LILLY AND COMPANY, una sociedad organizada y existente bajo las leyes de Indiana, con domicilio en Lilly Corporate Center, Indianapolis, Indiana 46285 USA, considerándose dicho cesionario de ahora en adelante el único y legal dueño y propietario de las solicitudes de patente en referencia.

TRADUCTOR OFICIAL

61

EN TESTIMONIO DE ELLO, se firma el presente documento el día 1 del mes de Marzo del año 2001.

LILLY FORSCHUNG GmbH.

Firma ilegible

Alyssa Kneisely

Director Administrativo

ELI LILLY AND COMPANY por el presente acepta dicha transferencia y traspaso.

EN TESTIMONIO DE ELLO, se firma el presente documento el día 27 del mes de Marzo del año 2001.

ELI LILLY AND COMPANY

Firmado ilegiblemente por Peter C. Stringer

Director Ejecutivo, Patentes Internacionales

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Registro Notarial 2001 No.890

Hay una relación de notarios y direcciones.

Por el presente certificamos que ante mí, Ulrike Glück, sustituto legal del Dr. Paul-Joachim von Wissel, un notario de Hamburgo Alemania, debidamente admitido y juramentado, compareció la Sra. Alyssa Kneisley, a quien conozco y me consta que está plenamente facultada y es la persona indicada en el Traspaso anterior y

65 62

firmante del mismo, quien declaró que otorgó dicho traspaso para los usos y objetivos allí expresados y por el presente lo ratifica, y que lo firmó por su propia mano y voluntariamente, en nombre del cedente identificado en el traspaso anterior.

En su condición de directora administrativa de la compañía de responsabilidad limitada denominada Lilly Forschung GmbH la señora Alyssa Kneisley está autorizada para representar sola a la compañía mencionada con pleno valor legal, la capacidad indicada fue establecida por mí mediante exámen de los registros comerciales que figuran en el Tribunal del Distrito de Hamburgo no. HR B 7º 269; la compareciente en su condición indicada está autorizada para firmar el documento adjunto.

Para constancia estampo mi firma y sello.

Hamburgo, Marzo 1 de 2001.

Firmado ilegiblemente

Sello en relieve en idioma alemán estampado sobre una lámina de papel rojo ligando el traspaso, el certificado notarial y la Apostilla por medio de una cuerda.

A CONTINUACIÓN ESTÁ LA APOSTILLA ESTABLECIDA EN LA CONVENCIÓN DE LA HAYA DE OCTUBLE 5 DE 1961 ESCRITA EN ALEMÁN. NO.9101 E/I – 335/2001 FIRMADA POR GÖRRES-OHDE, CON SELLO LANDGERRICHT HAMBURG – 128 HAMBURG CON FECHA MARZO 6 DE 2001.

= = = = = =

RICAURTE
TRADUCTOR OFICIAL
8887 Ministerio de Justicia

63

CERTIFICADO NOTARIAL

ESTADO: Indiana

CONDADO. Marion

En este día 27 de Marzo de 2001 compareció personalmente ante mí el citado P.G Stringer, quien declaraó que firmó el documento voluntariamente para los fines allí especificados.

Firmado: Catherine Michel

NOTARIO PUBLICO

Catherine Michel

Mi Comisión Expira en Octubre 21 de 2008

Residente en el Condado de Johnson

Sello de caucho: - Notario Público – Indiana – Sello

= = = = = =

SECRETARÍA DE ESTADO

ESTADO DE INDIANA

APOSTILLA

(Convención de La Haya de octubre 5 de 1961)

1. País: Estados Unidos de América

   Este Documento Público

2. ha sido firmado por Catherine Michel

3. actuando en su condición de Notario Público en y para el Condado de Johnson

4. y tiene el sello/estampilla de Notario Público en y para el Estado de Indiana

CERTIFICADO

5. en Indianapolis, Indiana

6. el día Once de Abril del año 2001

7. por el Secretario de Estado Delegado de Indiana

8. No. A2001 - 2677

9. Sello/estampilla: Sello en relive, estampado sobre lámina de papel metalizado:

Sello del Estado de Indiana - 1816 -.con escudo en el centro.

10. Firma: Firmado con fcasímil: Todd Rokita – Secretario de Estado Delegado

La referencia a la Apostilla de Alemania está en la página 3. (En mayúsculas)

Es traducción fiel y completa, de la cual queda copia en el archivo de esta Oficina de Traducciones para su confrontación, a la cual me remito.

Derechos de traducción: $36.000

Bogotá, D.C., 27 de abril de 2001

TRADUCTOR OFICIAL

Ministerio de Justicia

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MINISTERIO DE RELACIONES EXTERIORES
4283354
CUYA FIRMA APARECE EN EL DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS

NO SE ASUME RESPONSABILIDAD DEL TEXTO
2001 APR 30 PM 1:04
JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.

Eli Lilly And Comp
01.001.346

COLOMBIA
Our Case: Z-1032

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PATENT ASSIGNMENT

The undersigned, LILLY FORSCHUNG GmbH, a corporation domiciled in Essener Strasse 93, 22419 Hamburg, GERMANY owner of GB Application Nos. 0002691.4 and 0019599.0, filed on February 4, 2000 and August 9, 2000 (respectively) does hereby fully transfer and assign the right to file a patent application corresponding to said GB applications in Colombia to ELI LILLY AND COMPANY, a corporation organized and existing under the laws of Indiana, domiciled in Lilly Corporate Center, Indianapolis, Indiana 46285 USA, the said assignee being considered from now as the sole and lawful owner and proprietor of the subject right.

IN WITNESS WHEREOF, the present document is hereby signed on the 1 day of the month of March the year 2001.

LILLY FORSCHUNG GmbH

Alyssa Kneisely
Managing Director

ELI LILLY AND COMPANY hereby accepts such transfer and assignment.

IN WITNESS WHEREOF, the present document is hereby signed on the 27 day of the month of March the year 2001.

ELI LILLY AND COMPANY

Peter G. Stringer
Executive Director, International Patents

66

DR. ERWIN TIEDAU
DR. ARNOLD SIEVEKING
DR. PAUL-JOACHIM V. WISSEL
DR. AXEL PFEIFER
DR. TIL BRÄUTIGAM
DR. JAN CHRISTOPH WOLTERS
- NOTARE -

Bergstrasse 11, 20095 Hamburg
Telefon: (040) 30 20 060
Telefax: (040) 30 20 06 35
E-Mail: info@notariat-bergstrasse.de

Not. Reg. 2001 No. 890

This is to certify that before me,Ulrike Glück, legal substitute of Dr. Paul-Joachim von Wissel,a notary in Hamburg, Germany,duly admitted and sworn in,there appeared
Mrs. Alyssa Kneisley,
to me known and known to me to be in full capacity and to be the person indicated in and who executed the foregoing Assignment,and who declared that she executes the said Assignment for the use and purpoes therein expressed and she hereby ratifies it, and that she signed by her own hand and will such Assignment ,in the name of the constituent identified in the foregoing assignment.
In her capacity of managing director of the company with limited liability under the style of Lilly Forschung GmbH Mrs.Alyssa Kneisley is authorized to represent said company alone with full legal effect,identified in her said capacity by my examination of the commercial register files of the District Court of Hamburg-file no. HR B 7o 269;the appearant is as such entitled to sign the attached document.
Witness my hand and seal.
Hamburg, March 1,2oo1

1831

70 67

Apostille

(Convention de La Haye du 5 octobre 1961)

1. Land: Bundesrepublik Deutschland

   Diese öffentliche Urkunde

2. ist unterschrieben von Ulrike Glück

3. in der Eigenschaft als amtlich bestellte Notarvertreterin

4. sie ist versehen mit dem Siegel/Stempel) des

   Notars Dr. Paul-Joachim von Wissel

   Bestätigt

5. in Hamburg 6. am 6. März 2001

7. durch die Präsidentin des Landgerichts

8. unter Nr. 9101 E/I –338/2001

9. Siegel/Stempel 10. Unterschrift

Landgericht Hamburg 128 Hamburg

Görres-Ohde

SECRETARY OF STATE
STATE OF INDIANA

Sue Anne Gilroy
Secretary of State

APOSTILLE

(Convention de la Haye du 5 Octobre 1961)

1. Country: United States of America
2. This public document has been signed by *Catherine Michel*
3. acting in the capacity of Notary Public In & For *Johnson* County
4. and bears the seal/stamp of Notary Public In & For the State of Indiana

Certified

5. at Indianapolis, Indiana
6. the *Eleventh* day of *April*, 2001
7. by Deputy Secretary of State of Indiana.
8. A2001- *2677*

9. Seal/Stamp

10. Signature:

Todd Rokita
Deputy Secretary of State

The State House, Indianapolis, Indiana 46204, (317) 232-6531, FAX (317) 233-3283

NOTARIAL CERTIFICATE

77 64

STATE: Indiana
COUNTY: Marion

On this 27 day March 2001, personally appeared before me the named P. G. Stringer, who acknowledged that he signed the document as his voluntary act for the purposes therein set forth.

NOTARY PUBLIC
Catherine Michel
My Commission Expires
October 21, 2008
Resident of Johnson County

(SEAL)