

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

E _____ S _____

SUPERINDUSTRIA Y COMERCIO

Radicación: 01002004 00000002

Folios: 38

Fecha (AMD): 2001-05-10 16:14:03

Trámite: 002 PATENTES D 1 REGISTRADO/ 329 COMPLETOS

Dependencia: 2820 DIVISION DE NUEVAS CREACIONES

Re P1.- UNIVERSITY OF MASSACHUSETTS.- Solicitud de
Patente de Invención para "USO DE GLUTAMINA PARA LA
PREVENCIÓN DE DIARREA DE INICIO TARDIO
INDUCIDA POR IRINOTECAN".- Clase A61.- Expediente
Numero 01-002.004.-

- 1 Me refiero a mi solicitud de fecha 12 de Enero de 2001
- 2 Anexos me permito presentar a usted
 - (1) Copia autentica, debidamente certificada de la solicitud de patente presentada para el invento arriba nombrado **respecto de la cual reclamo prioridad**, a saber la solicitud estadounidense número 09/484 962 de 18 de Enero de 2000, junto con su traducción simple 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 del señor Gabriel Rueda Chadid quien elaboró la traducción de la legalizaciones de la solicitud estadounidense número 09/484 962 de 18 de Enero de 2000,
 - (3) Documento que acredita el traspaso que el autor del invento de la referencia hacen a favor de mi representado, de sus derechos sobre el mismo, debidamente apostillado junto con

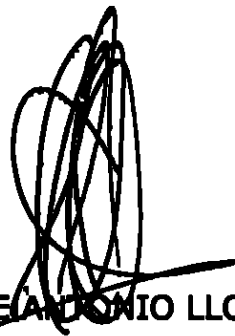
24 ~~27~~

su traducción oficial número 8252 debidamente legalizada hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número 428352 de 30 de Abril de 2001, y

- (4) Recibo Número 19,082, expedido por la Superintendencia de Industria y Comercio, que acredita el pago de la tasa de invocación de prioridad en el presente caso

3 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

SUPERINDUSTRIA Y COMERCIO
Radicación 01002004 00000002 Folios: 30
Fecha (AMD): 2001-05-10 16 14-03
Trámite 002 PATENTES D 1 REGISTRO/ 329 COMPLETEN
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

RECIBO OFICIAL DE CAJA 01 - 19,082
FECHA MARZO 23 DE 2001

***** CONSIGNACION *****

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

***** CONCEPTO *****

CANT	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		82 INVOCACION DE UNA PRIORIDAD EN NU	100,000 00
		TOTAL	\$ 100,000 00

SON CIENTO 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

26

EL SUSCRITO JEFE DEL AREA DE
LEGALIZACIONES DE MINISTERIO DE
RELACIONES EXTERIORES.

HACE CONSTAR

COMO NOTARIO SEXTO DE
SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA CON LA QUE SE
AUTENTICA QUE HE TENIDO A VISTA
13 DIC 2000

Que el señor Gabriel Rueda, se encuentra debidamente
registrado ante este Ministerio como traductor e
interprete oficial para los idiomas INGLES -ESPAÑOL,
ESPAÑOL - INGLES

Para efectos de esta certificación, el interesado presentó
copia autenticada de la resolución del Ministerio de
Justicia acerca de la vigencia de la resolución 1588
1982

COMO NOTARIO SEXTO DE
SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA CON LA QUE SE
AUTENTICA QUE HE TENIDO A VISTA
21 FEB 2001
21 AGO 1998

Dada en Santafe de Bogota, D. C., a los diez y nueve días
(19) del mes de diciembre de 1998

Neilson Sánchez Torres
Jefe Area de Legalizaciones

COMO NOTARIO SEXTO ENCARGADO DEL DEPARTAMENTO
DE SANTAFE DE BOGOTA, HAGO CONSTAR QUE
LA FOTOCOPIA AUTENTICA QUE HE TENIDO A VISTA

01 JUL 1998

01 SEP 2000

COMO NOTARIO SEXTO DE
SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA CON LA QUE SE
AUTENTICA QUE HE TENIDO A VISTA
13 DIC 2000

NST/ACM



Ministerio de Justicia y del Derecho

EL SECRETARIO GENERAL DEL MINISTERIO DE
JUSTICIA Y DEL DERECHO

CERTIFICA

Que por Resolución 5996 del 29 de noviembre de 1982, le fue expedida licencia para ejercer funciones de Traductor e Interprete Oficial en los idiomas INGLES-ESPAÑOL, ESPAÑOL-INGLES a GABRIEL RUEDA CHADID, identificado con la cedula de ciudadanía No 17 124 145 expedida en Bogotá. Que dicha resolución se encuentra vigente en la fecha

A solicitud del interesado, en Santafé de Bogotá, los 29 de agosto de 1998

JORGE LOIS SARRAGAL SARRAGAL

COMO SECRETARIO GENERAL DEL MINISTERIO DE JUSTICIA Y DEL DERECHO
HAGO CONSTAR
QUE LA FOTOCOPIA CONCORDA CON LA FOTOCOPIA ORIGINAL QUE ME ENVIARON
13 JUL 2000

COMO SECRETARIO GENERAL DEL MINISTERIO DE JUSTICIA Y DEL DERECHO
HAGO CONSTAR
QUE LA FOTOCOPIA CONCORDA CON LA FOTOCOPIA ORIGINAL QUE ME ENVIARON
13 JUL 2000

COMO SECRETARIO GENERAL DEL MINISTERIO DE JUSTICIA Y DEL DERECHO
HAGO CONSTAR
QUE LA FOTOCOPIA CONCORDA CON LA FOTOCOPIA ORIGINAL QUE ME ENVIARON
01 SET 1998

28 13

TRIBUNAL SUPERIOR DEL DISTRITO JUDICIAL DE SANTAFÉ DE BOGOTÁ
SECRETARIA GENERAL

LA SUSCRITA SECRETARIA DEL H TRIBUNAL SUPERIOR DEL DISTRITO JUDICIAL
DE SANTAFÉ DE BOGOTÁ,

COMO NOTARIO SEXTO DE
SANTAFÉ DE BOGOTÁ
HAGO CONSTAR
QUE LA FOTOCOPIA CONFORME CON LA FOTOCOPIA
AUTÉNTICA QUE ME TENGO A LA VISTA
13 DIC 2000

CERTIFICA

Que el Acuerdo No 183 de diciembre 3 de 1982 emanado de esta Corporación, por medio del cual dió posesión al señor GABRIEL RUEDA CHADID, identificado con Cédula de Ciudadanía número 145 de Bogotá, como TRADUCTOR E INTERPRETE OFICIAL EN IDIOMAS INGLÉS-ESPAÑOL, en virtud de la Resolución No. 1996-001-1998, es VIGENTE.

COMO NOTARIO SEXTO DE
SANTAFÉ DE BOGOTÁ
HAGO CONSTAR
QUE LA FOTOCOPIA CONFORME CON LA FOTOCOPIA
AUTÉNTICA QUE ME TENGO A LA VISTA
01 SET 2000
24 AGO 1998
PABLO MEJÍA BARAJAS

Se expide en Santafé de Bogotá D.C., a dieciseis (16) de noviembre
de mil novecientos noventa y cuatro (1994).

MARIA INES RODRIGUEZ TORRES
SECRETARIA

CRM /

COMO NOTARIO SEXTO DE
SANTAFÉ DE BOGOTÁ
HAGO CONSTAR
QUE LA FOTOCOPIA CONFORME CON LA FOTOCOPIA
AUTÉNTICA QUE ME TENGO A LA VISTA
SANTAFÉ DE BOGOTÁ
08 SET 1998

COMO NOTARIO SEXTO DE
SANTAFÉ DE BOGOTÁ
HAGO CONSTAR
QUE LA FOTOCOPIA CONFORME CON LA FOTOCOPIA
AUTÉNTICA QUE ME TENGO A LA VISTA
SANTAFÉ DE BOGOTÁ
01 JUL 1998
MANUEL ESTEBAN VILLALBA
NOTARIO
PABLO MEJÍA BARAJAS
HAGO CONSTAR
QUE LA FOTOCOPIA CONFORME CON LA FOTOCOPIA
AUTÉNTICA QUE ME TENGO A LA VISTA
SANTAFÉ DE BOGOTÁ
01 JUL 1998
08 SET 1998
SANTAFÉ DE BOGOTÁ
1910

REF: LLC-0034-2001 La presente es Traducción Oficial de un documento presentado originalmente en inglés Esta traducción es elaborada por Gabriel Rueda Chadid (Traductor Oficial)

ESTADOS UNIDOS DE AMERICA

A TODOS AQUELLOS QUE LLEGAREN A LEER EL CONTENIDO DEL

PRESENTE DOCUMENTO LES CERTIFICAMOS:

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS

Oficina de Marcas y Patentes de los Estados Unidos

Febrero 09, 2001

Se certifica que anexo se encuentra fiel copia de los Registros de la Oficina de Marcas y Patentes de los Estados Unidos correspondientes a los documentos de la patente solicitada y cuya identificación aparece más adelante, la cual cumplió con los requerimientos exigidos para que se otorgue una fecha de presentación de acuerdo con los dispuesto en la Sección 35 USC 111

Número de Solicitud: 09/484 982

Fecha de presentación: Enero 18, 2000

Por autorización del

COMISIONADO DE MARCAS REGISTRADAS Y PATENTES

T. WALLACE

Funcionario Encargado de Certificaciones (Hay firma y sello)

Enero 18, 2000

Expediente No. 07917-109001

Box Patent Application (Casilla de Solicitud de Patente)

Comisionado Adjunto de Patentes

Washington, DC 20231

Se radica una nueva solicitud original de patente que corresponde a

Solicitante Diane Savarese

Título PREVENCIÓN POR GLUTAMINA DE LA DIARREA DE APARICIÓN
TARDÍA INDUCIDA POR IRINOTECAN

Se incluyen los siguientes documentos, junto con los que se exigen para que se otorgue fecha de radicación según lo dispuesto en la sección 37 CFR 1.53(b)

	<u>Páginas</u>
Especificaciones	9
Reivindicaciones	2
Resumen	1
Declaración	[Se presentará en fecha posterior]

Además de las páginas indicadas, se adjunta en el present documento los siguientes ítems

- Tarjeta Postal

CERTIFICADO DE ENVÍO POR CORREO EXPRESO (37 CFR 1.10)

No de Etiqueta de Correo Expreso: EL224673832US,

Certifico que los siguientes documentos en relación con la

31 34

solicitud mencionada fueron depositados en el servicio postal de los Estados Unidos, correo Expreso Oficina Postal al Destinatario en Washington, D C 20231

Fecha de Depósito Enero 18, 2000 Hay firma

Esta solicitud recibe la clasificación de pequeña empresa Se radicará la respectiva declaración posteriormente Los derechos de presentación fueron calculados de la siguiente forma

Derechos básicos de presentación	\$345
Total de Reivindicaciones superiores a 20 por \$18	\$0
Reivindicaciones independientes superiores a 3 por \$78	\$0
Derechos para reivindicaciones dependientes múltiples	\$0
Total de derechos de presentación	\$345

Se adjunta cheque para cubrir los derechos de presentación. Favor aplicar otros derechos o créditos a la cuenta 06-1050 haciendo referencia al número de expediente que aparec citado anteriormente

Favor enviar toda correspondencia a

GARY L CREASON
Fish & Richardson P C
225 Franklin Street
Boston, MA 02110-2804

En caso de que este dinero sea incompleto, o si hay necesidad de conferencia por vía telefónica, favor comunicarse con el suscrito en el número (617) 542-5070

GABRIEL F. FLORES CHADIN
TRADUCTOR OFICIAL
RESOLUCION 1996 DE NOV 29-81
MINISTERIO DE JUSTICIA

32 55

Favor acusar recibo de esta solicitud mediante la devolución
de la tarjeta adjunta

Atentamente,

Firmado por: Gary L Creason

Registro No 34 310

Adjunto

WEB/mgc

CABRIEL RUEDA CHADIN
TRADUCTOR OFICIAL
RESOLUCION 5996 DE NOV 29-83
MINISTERIO DE JUSTICIA

33 36

REIVINDICACIONES

1 Un método quimioterapéutico que comprende la administración a un mamífero de una cantidad terapéuticamente eficaz de irinotecan, y la administración de una cantidad eficaz de glutamina antes de la aparición de la diarrea de aparición tardía inducida por el irinotecan

2 El método descrito en la reivindicación 1, donde la glutamina se administra por vía enteral

3 El método descrito en la reivindicación 1, donde el mamífero es un humano

4 El método descrito en la reivindicación 1, donde la dosificación de glutamina está entre 10 y 150 gramos por día

5 El método descrito en la reivindicación 4, donde la dosificación de glutamina está entre 20 y 60 gramos por día.

6 El método descrito en la reivindicación 5, donde la dosificación de glutamina es de aproximadamente 30 gramos por día

7 El método descrito en la reivindicación 4, donde la dosificación de glutamina se divide en 2 a 12 dosis individuales administradas periódicamente durante el día

8 El método descrito en la reivindicación 7, donde la dosificación de glutamina consiste en 3 dosis de

aproximadamente 30 gramos cada una

9 El método descrito en la reivindicación 1, donde la glutamina se administra en los días que incluyen el 1 y el 2, donde el día 1 es aquel en el cual se administra el irinotecan

10 El método descrito en la reivindicación 9, donde la dosificación de glutamina se administra los días 1, 2 y 3, donde el día 1 es aquel en el cual se administra el irinotecan

11 El método descrito en la reivindicación 1, donde la glutamina se administra en una formulación que comprende la Vitamina A

12 El método descrito en la reivindicación 1, donde la glutamina se administra en una formulación que comprende la Vitamina C

13 El método descrito en la reivindicación 1, donde la glutamina se administra en una formulación que comprende la Vitamina E

14 El método descrito en la reivindicación 1, donde la glutamina se administra en una formulación que comprende proteína

15 El método de la reivindicación 1, donde la glutamina se administra en una formulación que comprende

35 38
selenio

16 El método descrito en la reivindicación 9, donde la glutamina se administra en una formulación que comprende Vitaminas A, C y E

17 Un método para prevenir o reducir el desarrollo de diarrea de aparición tardía, inducida por irinotecan, que comprende la identificación de un mamífero en riesgo de diarrea de aparición tardía, inducida por irinotecan y la administración al mamífero de una cantidad eficaz de glutamina antes de la aparición de la diarrea de aparición tardía inducida por irinotecan

18 El método descrito en la reivindicación 17, donde el mamífero es paciente humano

19 Un método para el tratamiento de la diarrea existente, de aparición tardía, inducida por irinotecan, que comprende la administración de una cantidad eficaz de glutamina a un mamífero que muestre signos o síntomas de diarrea de aparición tardía, inducida por irinotecan

20 El método descrito en la reivindicación 19, donde el mamífero es paciente humano

GABRIEL RUEDA CHADIN
TRADUCTOR OFICIAL
RESOLUCION 5996 DE NOV 20-88
MINISTERIO DE JUSTICIA

36 39

Expediente N .: 07917-109001

Referencia del Cliente No.: UPMC 00-10

DECLARACION CONJUNTA Y PODER DE REPRESENTACION

En mi condición de inventor, declaro lo siguiente

Mi lugar de residencia, dirección postal y ciudadanía son las que aparecen al pie de mi nombre

Considero que soy el original, primero y único inventor (si tan solo aparece un nombre a continuación), o que somos los inventores originales, primeros y conjuntos (si se presenta numero plural de nombres) del asunto que se reivindica y por el cual se tramita patente sobre el invento titulado **PREVENCION POR GLUTAMINA DE LA DIARREA DE APARICION TARDIA INDUCIDA POR IRINOTECAN**, cuya especificación

[X] se adjunta al presente documento

Declaro que he revisado y comprendido el contenido de las especificaciones antes señaladas, incluyendo sus reivindicaciones, y modificaciones a las cuales se les ha hecho referencia

Soy consciente de mi obligatoriedad de divulgar toda información que este en mi poder y que resulte material para la patentabilidad de acuerdo con lo establecido en el Título 37, Código de Regulaciones Federales 1 56

Mediante el presente acto nombro a los siguientes apoderados y/o representantes para que tramiten la siguiente

37 48

solicitud y realicen todas las gestiones ante la Oficina de Marcas y Patentes a que haya lugar:

Gary L Creason, Reg No 34 310

J Peter Fasse, Reg No 32 983

John W Freeman, Reg No 29 066

John F Hayden, Reg No 37 640

Dirigir todas las llamadas telefónicas a GARY L. CREASON, en el número (617) 542-5070

Dirigir toda la correspondencia a GARY L CREASON a

FISH & RICHARDSON P C

225 Franklin Street

Boston, MA 02110-2804

Declaro igualmente que todo cuanto se ha expresado en esta documentación es cierto de acuerdo con mi saber y atender y con respecto de la información que poseo de la cual hay veracidad, además declaro que esta información la rindo bajo el conocimiento de que los testimonios en falso y similares son sancionados por la ley con multa o pena privativa de la libertad, o ambos de acuerdo con lo dispuesto en la Sección 1001 del Título 18 del Código de los Estados Unidos, y que tales declaraciones en falso en forma voluntaria pueden obstaculizar la validez de la solicitud o de la patente que se expida con base en tal información

Nombre completo del Inventor Diana Savarese

Firma del inventor: _____ Fecha: _____

Residencia 2 Taddeus Mason Road, Northboro, Massachusetts
01532

Ciudadanía Estados Unidos de América

33 44

Dirección Postal 2 Taddeus Mason Road. Northboro.
Massachusetts 01532

La anterior es Traducción Oficial de un documento presentado originalmente en inglés Esta traducción fue realizada por GABRIEL RUEDA CHADID (Traductor Oficial) Resolución 5996 del Minjusticia, por lo cual estampo mi Sello y Firmo

Bogotá D C , Abril 26 del 2001

44

GABRIEL RUEDA CHADID
TRADUCTOR OFICIAL
RESOLUCION 5996 DE NOV 20-99
MINISTERIO DE JUSTICIA

FOOD FOR UNIVERSITY
Massachusetts
01 002 004 AT
39

PA 364716

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

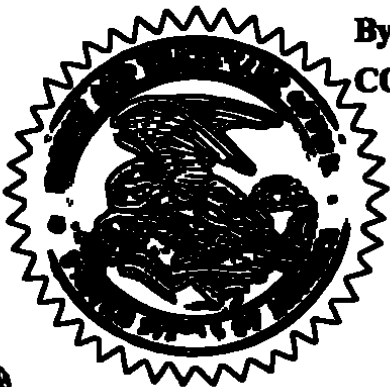
February 09, 2001

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM
THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK
OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT
APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A
FILING DATE UNDER 35 USC 111

APPLICATION NUMBER 09/484,962

FILING DATE January 18, 2000

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS



T. Wallace
T WALLACE
Certifying Officer

01-19-00

FISH & RICHARDSON P C

225 Franklin Street
Boston, Massachusetts
02110-2804

Telephone
617 543-9070

Facsimile
617 543-8906

Web Site
www.fr.com

January 18, 2000

Attorney Docket No 07917-109001

Box Patent Application
Assistant Commissioner for Patents
Washington, DC 20231

PTO
09/484962
01/18/00

BOSTON

DELAWARE

NEW YORK

SILICON VALLEY

SOUTHERN CALIFORNIA

TWIN CITIES

WASHINGTON DC

Presented for filing is a new original patent application of

Applicant Diane Savarese

Title v GLUTAMINE PREVENTION OF DELAYED-ONSET, IRINOTECAN-INDUCED DIARRHEA

Enclosed are the following papers, including those required to receive a filing date under 37 CFR 1.53(b)

	Pages
Specification	9
Claims	2
Abstract	1
Signed Declaration	[To be Filed at a Later Date]

In addition to the above-listed pages, the following items are also enclosed herewith

- Postcard

CERTIFICATE OF MAILING BY EXPRESS MAIL

Express Mail Label No. EL7246738321J8

I hereby certify under 37 CFR §1.10 that this correspondence is being deposited with the United States Postal Service as Express Mail Post Office to Addressee with sufficient postage on the date indicated below and is addressed to the Assistant Commissioner for Patents, Washington D C 20231

January 18, 2000

Date of Deposit

Signature

Samantha Bell
Typed or Printed Name of Person Signing Certificate

FISH & RICHARDSON P C

Assistant Commissioner for Patents
January 18, 2000
Page 2

41 44

\ The present application is entitled to small entity status A small entity statement will be filed at a later date The filing fee has been calculated as follows

Basic filing fee	\$345
Total claims in excess of 20 times \$18	\$0
Independent claims in excess of 3 times \$78	\$0
Fee for multiple dependent claims	\$0
Total filing fee	\$345

A check for the filing fee is enclosed. Please apply any other required fees or any credits to Deposit Account No 06-1050, referencing the attorney docket number shown above.

Please send all correspondence to

GARY L CREASON
Fish & Richardson P C
225 Franklin Street
Boston, MA 02110-2804

If this application is found to be incomplete, or if a telephone conference would otherwise be helpful, please call the undersigned at (617) 542-5070

Kindly acknowledge receipt of this application by returning the enclosed postcard

Respectfully submitted,



Gary L. Creason
Reg No 34,310

Enclosures

GLC/lxf

20017554 doc

008110-29648460

42 45

**APPLICATION
FOR
UNITED STATES LETTERS PATENT**

TITLE: **Glutamine Prevention of Delayed-Onset, Irinotecan-Induced Diarrhea**

APPLICANT: **Diane Savarese**

CERTIFICATE OF MAILING BY EXPRESS MAIL

Express Mail Label No. EL22467383245

I hereby certify under 37 CFR §1.10 that this correspondence is being deposited with the United States Postal Service as Express Mail Post Office to Addressee with sufficient postage on the date indicated below and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231

January 19, 2000
Date of Deposit

Samantha Bell
Signature

Samantha Bell
Typed or Printed Name of Person Signing Certificate

008770-29648460

43

43

GLUTAMINE PREVENTION OF DELAYED-ONSET IRINOTECAN-INDUCED DIARRHEA

TECHNICAL FIELD

This invention relates to oncology and gastroenterology, and more particularly to chemotherapy involving irinotecan

BACKGROUND

Irinotecan hydrochloride (CPT-11, Camptosar ®, Pharmacia & Upjohn) is a chemotherapeutic agent that displays activity against a broad spectrum of malignancies, including carcinomas of the colon, stomach and lung. Irinotecan is FDA-approved for treatment of metastatic colorectal cancer and is an important drug for the management of that disease (Rothenberg, et al, *J Clin Oncol* 14 1128-1135 (1996), Rougier et al, *J Clin Oncol* 15:251-260 (1997), Rothenberg et al, *Seminars in Oncology* 26 632-639 (1999)). Diarrhea is a common side effect of irinotecan. Frequently the diarrhea is of sufficient severity to necessitate limitation of irinotecan dosage to sub-optimal levels.

Irinotecan-associated diarrhea is classified into two types, i.e., early and delayed-onset (late). These two types of irinotecan-associated diarrhea are treated differently. Early diarrhea, typically observed within 24 hours after irinotecan infusion, is cholinergically mediated, short lasting and prevented by atropine administration. (Saliba et al., *J Clin Oncol* 16 2745-2751 (1998)). Delayed-onset, irinotecan-induced diarrhea is multifactorial, with contributions from dysmotility and secretory factors as well as a direct toxic effect of the drug or a metabolite known as SN-38, on the intestinal mucosa (Saliba et al *supra*, Hecht et al, *Oncology* 12 (Suppl 6) 72-78 (1998)). Both irinotecan and SN-38 undergo enterohepatic recirculation, and the concentration of SN-38 has been correlated with diarrhea in humans (Sasaki et al, *Japan. J Cancer Res* 86 101-110 (1995), Kudoh et al *Japan J Cancer Res* 86 406-413 (1995)). Time of onset and duration of delayed-onset, irinotecan-induced diarrhea varies with the dosing schedule (Pitot et al, *J Clin Oncol* 15 2910-2919 (1997)) and age. Patients over 65 years of age are at increased risk for severe diarrhea (Rougier et al, *supra*, Pitot et al, *supra*). In European studies in which patients received 350mg/m² q 3 weeks, the median time to onset was 5 days, and the median duration was 5 days (Rougier et al, *supra*). In American trials in which patients received 125mg/m²/week for 4/6 weeks, the median time to onset was 11 days, and median duration was 2 days (Pitot et al, *supra*).

008110-29648460

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Intensive loperamide treatment (2 mg every 2 hours until diarrhea-free for 12 hours) reduces the incidence of severe diarrhea (Abigerges et al, *J Natl Cancer Inst* 86 446-449 (1994), Camptosar® irinotecan HCl injection – Management of side effects, <http://www.meds.com/colon/camptosar/management.html>) A modification of this regimen, i.e., 4 mg to start, then 4 mg po every 4 hours, has become the standard of care in the US (Pharmacia-Upjohn, Irinotecan package insert) In one published study, the use of an intensive loperamide regimen was reported to decrease the incidence of grade 3-4 diarrhea from 56% of patients treated on a weekly x 4 schedule to 9% in one study (Conti et al, *J. Clin. Oncol.* 14 709-715 (1996))

Although loperamide and other opiates are useful for treating delayed-onset, irinotecan-induced diarrhea, this side effect still limits irinotecan dosage in many patients For such patients, a means of preventing, or an improved means of treating, delayed-onset, irinotecan-induced diarrhea would allow the anti-tumor potential of irinotecan to be utilized more fully

SUMMARY OF THE INVENTION

It has been discovered that administration of L-glutamine prevents or significantly reduces development of delayed-onset, irinotecan-induced diarrhea in cancer patients undergoing chemotherapy Accordingly, the invention provides a chemotherapeutic method. The method includes administering to a mammal, e.g., a human patient, a therapeutically effective amount of irinotecan, and administering an effective amount of glutamine prior to the onset of late-onset diarrhea induced by the irinotecan Preferably, the glutamine is administered enterally, e.g., orally Preferably, the glutamine is administered in a dosage of 10 to 150 grams per day More preferably, the dosage is 20 to 60 grams per day, e.g., approximately 40 or 50 grams per day In some embodiments, the glutamine dosage is approximately 30 grams per day Preferably, the daily dosage is administered in 2 to 12 individual doses. In some embodiments, the daily glutamine dosage is three oral doses of approximately 10 grams each. Preferably, the glutamine dosage is administered on days including days 1 and 2, with day 1 being the day on which the irinotecan is administered More preferably, the glutamine dosage is administered on days including days 1, 2 and 3, with day 1 being the day on which the irinotecan is administered The glutamine can be

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administered in a formulation, e.g., as a component in a composition containing vitamin A, vitamin C, vitamin E, or selenium, or a combination thereof.

The invention also provides a method of preventing or reducing development of delayed-onset, irinotecan-induced diarrhea. The method includes identifying a mammal, e.g., a human patient, at risk for delayed-onset, irinotecan-induced diarrhea, and administering to the patient an effective amount of glutamine prior to the onset of delayed-onset diarrhea induced by the irinotecan.

The invention also provides a method of treating existing, delayed-onset, irinotecan-induced diarrhea. The method includes administering an effective amount of glutamine to a mammal, e.g., a human patient, displaying signs of delayed-onset, irinotecan-induced diarrhea.

As used herein, "irinotecan" means irinotecan and pharmaceutically acceptable salts and metabolites thereof.

As used herein, "glutamine" means L-glutamine or DL-glutamine, excluding glutamine residues incorporated into proteins.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. In cases of conflict, the present application, including definitions, will control. All publications, patents, and other references mentioned herein are incorporated by reference.

The details of one or more embodiments of the invention are set forth in the detailed description below. Other features, objects, and advantages of the invention will be apparent from the detailed description and from the claims.

DETAILED DESCRIPTION

Use of irinotecan as a chemotherapeutic agent is known in the art. See, e.g., Pazdur, *Oncology* 12 (Suppl. 6) 13-21 (1998), Hecht et al., *Oncology* 12 (Suppl. 6) 72-78 (1998). Administration of irinotecan in the present invention can be carried out in accordance with established clinical practice, for example in the treatment of metastatic colorectal cancer. In some cases, however, the invention enables a clinician to prescribe an irinotecan dosage higher than in the prior art because of glutamine's alleviation of irinotecan-induced diarrhea.

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Using the present disclosure, such adjustment of irinotecan dosage can be accomplished by one of ordinary skill in the art, without undue experimentation

Glutamine (Gln, glutamic acid 5-amide) can be synthesized chemically or isolated from natural sources. Because the glutamine molecule contains a chiral center, it is optically active. Therefore, glutamine obtained by conventional chemical synthesis is a racemic mixture (DL-glutamine). When DL-glutamine is used, dosage should be adjusted to account for any difference in activity between the D and L isomers. In preferred embodiments of the invention, L-glutamine is used. L-glutamine is commercially available as a pure compound. Traditional diets taken by mouth normally contain less than 10 grams of glutamine per day (Hall et al, Br J Surg. 83 305-312 (1996)).

Supplemental glutamine can be administered enterally or parenterally. Solutions containing glutamine for enteral use have a limited shelf life, because glutamine decomposes into pyroglutamate and ammonia. Glutamine is stable in sterile nutrient solutions for at least 22 days when stored at 4°C (Hornsby-Lewis et al, *J Parenter Enteral Nutr* 18 268-273 (1994)). Although glutamine pills or capsules can be used in the present invention, they are expensive and contain small amounts of glutamine (500-1000 mg) relative to the daily dosages preferred in the practice of this invention. Powdered glutamine is preferred because it is inexpensive, easy to use, well absorbed, well tolerated, and safe. For information on the safety of orally administered and parenterally administered glutamine, see, e.g., Hall, Br J Surg 83 305-312 (1996), Ziegler et al, *Nutrition* 12(11-12 Suppl) S68-70 (1996), Ziegler et al, *J Parenter Enter Nutr* 14 137S-143S (1990).

Preferably, glutamine administration is enteral, with the total daily dosage being divided into separate doses administered over the course of the day. This promotes contact with the epithelial lining of the gut. A convenient and effective means of enteral administration is oral ingestion. Where indicated by the condition of the patient, enteral administration of glutamine can be by alternative means, for example by feeding tube.

Glutamine powder is practically tasteless. For enteral administration, glutamine powder can be mixed with food or beverage, or dissolved in water and flushed into a feeding tube. Such glutamine mixed with food or dissolved in liquid can be in the form of pure glutamine. Alternatively, glutamine for use in this invention can be formulated as an active ingredient in any pharmaceutically acceptable composition. Other components in a

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glutamine-containing composition can be of various types, including inert fillers, nutritional supplements, therapeutic agents, flavorings, food colorings and and preservatives. Such compositions can be prepared by any of the methods known in the art. Useful methods and compositions are described, for example, in *Remington's Pharmaceutical Sciences* (Mack Pub Co., Easton, PA, 1980). A convenient glutamine formulation suitable for use in the present invention is available commercially under the name "Glutamine Enriched Antioxidant Formula" (Cambridge Nutraceuticals, Cambridge, MA). This formulation is sold in individual packets, each containing 10 grams of L-glutamine, 10 grams of protein, 6,500 IU of vitamin A (as beta carotene), 200 mg of vitamin C (as ascorbic acid), 100 IU of vitamin E (as dl-alpha-tocopherol) and 50 mcg of selenium (as selenomethionine).

At glutamine doses of 0.57 g/kg and above, plasma ammonia concentrations may increase (Ziegler et al., *J Parenter Enteral Nutr* 14:137S-143S (1990)). Consequently, in cirrhotic patients such doses should be used with caution, and cirrhotic patients should be monitored appropriately. In some clinical circumstances the use of oral supplemental glutamine may be contraindicated. For example, it has been reported that intestinal glutamine catabolism is responsible for approximately 50% of the ammonia released into the portal vein (Weber et al., *J Lab. Clin. Med.* 94:27-41 (1979)). Thus, in patients with hyperammonemia and hepatic encephalopathy, glutamine dosage may need to be reduced.

The invention is further illustrated by the following examples. The examples are provided for illustration purposes only, and they are not to be construed as limiting the scope and content of the invention in any way.

Examples

Oral glutamine supplementation was administered to 5 cancer patients being treated with irinotecan. This alleviated delayed onset, irinotecan-induced diarrhea. This alleviation allowed full doses of irinotecan to be administered in subsequent chemotherapy.

The first patient, a 65 year-old man with 5-fluorouracil-refractory metastatic colon cancer, developed grade 4 diarrhea (as assessed according to National Cancer Institute Common Toxicity Criteria) requiring hospital admission for hydration and bowel rest 4 days after receiving the second week of his first cycle of irinotecan administered at 125mg/m²/week. Intensive loperamide treatment failed to control this patient's diarrhea. A

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two-week break was instituted, and he was retreated for the second cycle of chemotherapy with 100mg/m²/week resulting in grade 1 diarrhea only for the 4 weeks of therapy. For the next and all subsequent chemotherapy cycles, dose was re-escalated to 125mg/m²/week, but accompanied by glutamine administration. Ten grams of L-glutamine was administered orally, starting the morning of irinotecan treatment, and repeated every 8 hours thereafter for 48 hours. This series of glutamine doses was administered following each dose of irinotecan. The 10-gram dose of glutamine was formulated in a commercial product marketed under the name "Glutamine Enriched Antioxidant Formula" (Cambridge Nutraceuticals, Boston MA). The patient received 30 weeks of irinotecan therapy at full dose without recurrence of > grade 1 diarrhea. The glutamine was sufficient to achieve this level of diarrhea prevention without the use of loperamide. The patient's tumor was responding to the treatment after 2 cycles of irinotecan.

The second patient, a 56 year old woman with metastatic and locally recurrent rectal cancer, had an ileostomy with baseline daily firm stool output of <500cc/day. She received weekly irinotecan 125mg/m² after failing to respond to treatment with 5-fluorouracil. After the second week of therapy she was admitted to the hospital with grade 3 vomiting, grade 4 diarrhea, and >1500cc per day of watery stool per ileostomy despite taking up to 20 loperamide tablets (2 mg each) every 24 hours. She was intravenously rehydrated, and a new cycle of chemotherapy was instituted 2 weeks later at 100mg/m². This still resulted in grade 3 diarrhea, with >1500cc/day watery stool output via ileostomy. Glutamine at a dosage of 10 Gm po tid (Glutamine Enriched Antioxidant Formula, Cambridge Nutraceuticals, Cambridge, MA) was begun the night before she received her next weekly dose of irinotecan at 100mg/m². The patient continued taking 10 grams of glutamine every 8 hours for 6 additional doses after receiving each week's therapy. She continued to receive therapy at a dose of 100mg/m² with no watery ileostomy output.

Three additional patients have been treated. All three were receiving irinotecan therapy for metastatic colorectal cancer. With all three patients, severe diarrhea necessitated limiting irinotecan dosage below 125 mg/m². By taking 10 grams of glutamine, 3 times per day during the three days following irinotecan treatment, all three patients were able to re-escalate irinotecan dose up to 125mg/m² during subsequent courses of chemotherapy.

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The following is a protocol for a larger study of the use of glutamine to alleviate late-onset diarrhea associated with irinotecan therapy. The objectives of the study include obtaining further data on the effectiveness of glutamine in the prevention of late-onset, irinotecan-induced diarrhea, obtaining further information on the ability of glutamine to allow dose re-escalation of irinotecan to standard doses, obtaining further information on potential side effects of glutamine administration in the context of irinotecan therapy, and obtaining further information on the efficacy of irinotecan in therapy of metastatic colorectal cancer in patients receiving oral glutamine, including response rate and time to progression.

Eligibility criteria for participation in the study will be documented malignancy for which irinotecan therapy is being used, either weekly, or every 3 weeks, late diarrhea related to irinotecan, beginning more than 24 hours after receiving irinotecan, and grade 2 or greater; no chronic diarrheal illness (more than 4 stools per day for >4 weeks), medical and psychiatric condition sufficient to tolerate therapy; and no concurrent radiation to the abdomen. Patients deemed eligible will have their most recent dose level of irinotecan recorded and must have recovered from irinotecan toxicity to grade 1 diarrhea. The therapy of that episode of diarrhea must have concluded.

Patients enrolled in the study initially will be treated at a lower dose of irinotecan than that which caused the diarrhea during the prior treatment, as indicated below.

Table 1 Patients receiving weekly therapy

Dose of irinotecan which resulted in at least grade 2 diarrhea	Dose of irinotecan to be used for next two weeks in combination with oral glutamine
125mg/m ²	100mg/m ²
100mg/m ²	75mg/m ²
75mg/m ²	50mg/m ²

Table 2 Patients receiving irinotecan therapy every 3 weeks

Dose of irinotecan which resulted in at least grade 2 diarrhea	Dose of irinotecan to be used for next cycle in combination with oral glutamine
350mg/m ²	325mg/m ²
325mg/m ²	300mg/m ²
300mg/m ²	275mg/m ²
275mg/m ²	250mg/m ²
250mg/m ²	225mg/m ²

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Each 10-gram glutamine dose will be in the form of Glutamine Enriched Antioxidant Formula (Cambridge Nutraceuticals, Boston MA) Each dose of glutamine will be mixed in cold non-adidic liquid and drunk quickly The glutamme will be administered orally, in 10-gram doses, 3 times per day for 2 or 3 days following each dose irinotecan

Subsequent irinotecan dose re-escalation for patients receiving weekly therapy will be as follows Patients will receive two weekly courses at the dose level indicated above. Patients then will undergo dose re-escalation as indicated below, as long as the patient has not experienced greater than grade 1 diarrhea.

Table 3 For patients receiving weekly therapy

Initial dose of irinotecan with glutamine supplementation	Dose of irinotecan to be used for remainder of that cycle in combination with oral Gln
100mg/m2	125 mg/m2
75mg/m2	100mg/m2

Subsequently, if two additional weeks of therapy are administered without worse than grade 1 diarrhea, then dose may be re-escalated again to a maximum of 125mg/m2/week

Re-escalation of irinotecan dosage for patients receiving every 3-week therapy cycles will be as indicated in Table 4 below

Table 4 Patients receiving every 3 weekly therapy

Dose of irinotecan with glutamine supplementation	Dose of irinotecan to be used for the next cycle with Glutamine oral supplementation
325mg/m2	350 mg/m2
300mg/m2	325mg/m2
275mg/m2	300 mg/m2
250mg/m2	275mg/m2

In subsequent cycles, dose may be re-escalated again, if no greater than grade 1 diarrhea occurs, to a maximum of 350mg/m2 every 3 weeks

Management of breakthrough diarrhea will be as follows All patients in the study will be counseled promptly regarding the use of intensive loperamide therapy if severe diarrhea occurs If loperamide fails to control the diarrhea, then further treatment will be at the discretion of the treating physician Patients will need to be taken off therapy if greater

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than grade 2 diarrhea develops in spite the use of oral glutamine, and further management of the patients will be at the discretion of the treating physician.

Toxicities from oral glutamine are not expected. If patients have recurrence of grade 2 or greater diarrhea in spite of the use of oral glutamine supplements, they will be removed from protocol therapy, and further management will be at the discretion of the treating physician.

No laboratory studies or radiographic studies will be required for participation in this protocol. Patients will be followed by their regular treating doctor throughout the course of the therapy. Patients will be followed in the study for as long as they continue to receive irinotecan.

Patients will be assessed for diarrhea and any other toxic side effects weekly while they continue to receive irinotecan, or every 3 weeks if they are receiving therapy on an every 3 week basis.

If patients have recurrence of > grade 2 diarrhea despite the use of oral glutamine supplements, they will be removed from protocol therapy, and further management will be at the discretion of the treating physician.

A number of embodiments of the invention have been described. Nevertheless, it will be understood that various modifications may be made without departing from the spirit and scope of the invention. Accordingly, other embodiments are within the scope of the following claims.

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WHAT IS CLAIMED IS

- 1 A chemotherapeutic method comprising administering to a mammal a therapeutically effective amount of irinotecan, and administering an effective amount of glutamine prior to onset of delayed-onset diarrhea induced by the irinotecan.
- 2 The method of claim 1, wherein the glutamine is administered enterally
- 3 The method of claim 1, wherein the mammal is a human.
- 4 The method of claim 1, wherein glutamine dosage is from 10 to 150 grams per day
- 5 The method of claim 4, wherein the glutamine dosage is from 20 to 60 grams per day
- 6 The method of claim 5, wherein the glutamine dosage is approximately 30 grams per day
- 7 The method of claim 4 wherein the glutamine dosage is divided into 2 to 12 individual doses administered periodically during the day
- 8 The method of claim 7, wherein the glutamine dosage consists of 3 doses of approximately 30 grams each.
- 9 The method of claim 1, wherein the glutamine is administered on days including days 1 and 2, day 1 being the day on which the irinotecan is administered.
- 10 The method of claim 9, wherein the glutamine dosage is administered on days including days 1, 2 and 3, day 1 being the day on which the irinotecan is administered
- 11 The method of claim 1 wherein the glutamine is administered in a formulation comprising vitamin A.
- 12 The method of claim 1, wherein the glutamine is administered in a formulation comprising vitamin C

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- 13 The method of claim 1, wherein the glutamine is administered in a formulation comprising vitamin E
- 14 The method of claim 1, wherein the glutamine is administered in a formulation comprising protein.
- 15 The method of claim 1, wherein the glutamine is administered in a formulation comprising selenium.
- 16 The method of claim 9, wherein the glutamine is administered in a formulation comprising vitamins A, C and E
- 17 A method of preventing or reducing development of delayed-onset, irinotecan-induced diarrhea, comprising identifying a mammal at risk for delayed-onset, irinotecan-induced diarrhea, and administering to the mammal an effective amount of glutamine prior to onset of delayed-onset diarrhea induced by the irinotecan
- 18 The method of claim 17, wherein the mammal is a human patient.
- 19 A method of treating existing, delayed-onset, irinotecan-induced diarrhea, comprising administering an effective amount of glutamine to a mammal displaying signs or symptoms of delayed-onset, irinotecan-induced diarrhea.
- 20 The method of claim 19, wherein the mammal is a human patient.

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ABSTRACT

A chemotherapeutic method that prevents or reduces development of late-onset, irinotecan-induced diarrhea is disclosed. The method includes administering glutamine in association with irinotecan. A method of preventing or treating late-onset, irinotecan-induced diarrhea also is disclosed. The method includes identifying a patient at risk for delayed-onset, irinotecan-induced diarrhea, and administering an effective amount of glutamine prior to onset of late-onset diarrhea induced by the irinotecan. Examples of the invention are disclosed in which oral glutamine was effective when administered at a rate of three 10-gram doses per day, on days 1 and 2, with day 1 being the day on which irinotecan is administered

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As a below named inventor I hereby declare that:

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I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled, **GLUTAMINE PREVENTION OF DELAYED-ONSET IRINOTECAN INDUCED DIARRHREA**, the specification of which

- ☒ is attached hereto.
☐ was filed on _ as Application Serial No _ and was amended on _____
☐ was described and claimed in PCT International Application No. _____ filed on _____ and as amended under PCT Article 19 on _____

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above

I acknowledge the duty to disclose all information I know to be material to patentability in accordance with Title 37, Code of Federal Regulations, §1.56.

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Full Name of Inventor Diane Savarese

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Secretario de Estado

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personally appeared before me, a Notary Public,

a quien doy fé de conocer y me consta que
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Diane Savarese

Diane Savarese

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Irinotecan-Induced Diarrhea

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2 **has been signed by** Jennifer M. Nadeau

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4 **in the state of Massachusetts, whose commission expires on**

January 31, 2003

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5 **at Boston, Massachusetts**

6 **on** April 5, 2001

by the Secretary of the Commonwealth
176695

9 **signed under the**

Great Seal of the Commonwealth

10 **Signature**

William Francis Galvin
William Francis Galvin
Secretary of the Commonwealth