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74. APODERADO ALVARO ORREA ORDONEZ

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Patente de Invención

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Patente de Modelo de Utilidad

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Capítulo II.

2

SOLICITANTE
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3

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Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página

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ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud
- ☐ Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica
- ☐ Poderes, si fuere el caso
- ☐ Documento de cesión del inventor al solicitante o a su causante
- ☐ Declaraciones
- ☒ Copia de la solicitud Internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen preliminar (IPEA)
- ☐ Traducción del examen preliminar internacional efectuado por la IPEA
- ☐ De ser el caso, copia del contrato de acceso
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- ☐ De ser el caso, certificado de depósito del material biológico
- ☐ Arte final 12 x 12
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud
- ☐ De ser el caso, modificaciones efectuadas a la solicitud internacional.
- ☒ Otros: ANEXOS VARIOS

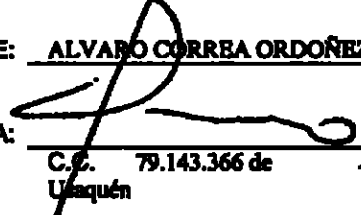
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FIGURA CARACTERISTICA

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NOMBRE: ALVARO CORREA ORDOÑEZ

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ANEXO - INVENTORES

TITULO: FÓRMULA POLIMÓRFICA CRISTALINA DE CLORHIDRATO DE IRINOTECAN

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(54) Title: CRYSTALLINE POLYMORPHIC FORM OF IRINOTECAN HYDROCHLORIDE

(57) Abstract: This invention relates to a novel crystalline polymorphic form of irinotecan hydrochloride. A process for preparing this novel polymorphic form, pharmaceutical compositions comprising it as an active ingredient and the use of the same and its pharmaceutical compositions as a therapeutic agent is also within the scope of the present invention.

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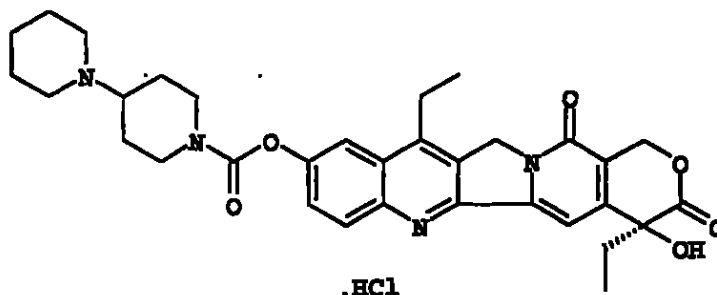
Crystalline polymorphic form of irinotecan hydrochloride

5 SUMMARY OF THE INVENTION

This invention relates to a novel crystalline polymorphic form of the compound (S)-4,11-Diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1 H-pyrano[3',4':6,7]-indolizino[1,2-b]quinolin-9-yl [1,4'-bipiperidine]-1'-carboxylate (irinotecan) hydrochloride. A process for preparing this novel polymorphic form, pharmaceutical compositions comprising it as an active ingredient and the use of the same and its pharmaceutical compositions as a therapeutic agent is also within the scope of the present invention.

BACKGROUND OF THE INVENTION

Irinotecan hydrochloride, the compound (S)-4,11-Diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1 H-pyrano[3',4':6,7]-indolizino[1,2-b]quinolin-9-yl [1,4'-bipiperidine]-1'-carboxylate hydrochloride, having the formula:



is a camptothecin analog and topoisomerase I inhibitor derived from a compound which occurs naturally in the Chinese tree, *Camptotheca acuminata*.

Since its approval in the United States in 1996, irinotecan hydrochloride trihydrate (CPT-11, CAMPTOSAR[®],

injection, Pharmacia Corp.; Peapack, NJ) has undergone extensive clinical evaluation. In the past five years, the focus of development has evolved from evaluation of single-agent activity in refractory disease settings to evaluation of front-line irinotecan-based combination chemotherapy regimens and integration of irinotecan into combined modality regimens. Important studies have been performed clarifying the role of irinotecan treating colorectal and other gastrointestinal cancers, small cell and non-small cell lung cancer, and a variety of other malignancies.

CPT-11 has shown activity against a variety of tumor types, particularly refractory colorectal tumors, and it is used for the treatment of various forms of cancer. Its primary use is in the treatment of colon cancer, particularly advanced colon cancer. It is also of interest for treatment of other cancers, such as cancers of the lung, the stomach and the pancreas.

CPT-11 is usually administered in one of two treatment regimens. In one regimen, a dose of $125\text{mg}/\text{m}^2$ of CPT-11 is given i.v. over a 90 minute period each week for four weeks. After a lapse of two weeks this is repeated, so that the patient receives CPT-11 in four weeks out of every six. In the other treatment regimen a dose of $350\text{mg}/\text{m}^2$ is given i.v. over 90 minutes, every third week. Thus, the one regimen operates with a six week cycle and the other regimen on a three week cycle.

CPT-11 is indicated as a component of first-line therapy in combination with 5-FU/LV for the treatment of patients with metastatic carcinoma of the colon or rectum. CPT-11 is also indicated for patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following initial 5-FU-based therapy. CPT-11

is the first topoisomerase I inhibitor with known activity in colorectal cancer, and the first FDA fully approved colorectal cancer treatment in over 40 years.

The antitumor activity of CPT-11 is attributed to an active metabolite, 7-ethyl-10-hydroxy 20(S)camptothecin (SN-38), which is produced after enzymatic cleavage by carboxylesterases in the liver, small intestine and plasma. SN-38 is 100-fold more cytotoxic than CPT-11.

CPT-11 (CAMPTOSAR®) is supplied as a sterile, pale yellow, clear, aqueous solution. It is available in two single-dose sizes: 2 ml-fill vials contain 40 mg irinotecan hydrochloride and 5 ml-fill vials contain 100 mg irinotecan hydrochloride. Each milliliter of solution contains 20 mg of irinotecan hydrochloride (on the basis of the trihydrate salt), 45 mg of sorbitol powder, and 0.9 mg of lactic acid. The pH of the solution has been adjusted to 3.5 (range, 3.0 to 3.8) with sodium hydroxide or hydrochloric acid. CAMPTOSAR® is intended for dilution with 5% dextrose injection (D5W), or 0.9% sodium chloride injection, prior to intravenous infusion. The preferred diluent is 5% dextrose injection.

Yakult US patent No. 4,604,463 describes a broad family of camptothecin derivatives including irinotecan, its pharmaceutically acceptable salts and preparation thereof.

Pharmacia & Upjohn Co. US patent No. 6,121,451 discloses intermediates and processes for the synthesis of camptothecin derivatives, such as irinotecan hydrochloride.

Pharmacia and Upjohn S.p.A. International patent applications No. WO 01/10443 and WO 01/30351 describe oral

pharmaceutical preparations comprising irinotecan hydrochloride.

Sawada et al., Chem. Pharm. Bull. Vol. 39, No. 6, 1446-54 (1991), describes the preparation of irinotecan from natural camptothecin in five chemical steps and 20% of overall yields. Sawada further discloses the crystal structure of irinotecan hydrochloride trihydrate (also known as CPT-11 that is the one that is currently used for the manufacturing of the commercially available product), as slightly pale yellow needles or crystalline powder by crystallization from water. The product is then dried (in vacuo) and equilibrated in a 75% relative humidity chamber for 70 hours. Crystalline form of irinotecan hydrochloride trihydrate as described by Sawada et al. is herein after referred to, for convenience, as "Form b".

A summary of the physical properties of Form b are reported below.

Infrared absorbtion

IR (KBr) ν : 1748 (lactone carbonyl), 1688 (carbamate carbonyl), 1663 (pyridone carbonyl), cm^{-1} .

Water solubility

Water solubility of Form b is at room temperature of about 10 mg/mL.

Powder X-ray diffraction (PXRD)

Form b was also characterized by its powder X-ray diffraction pattern, as shown in the spectrum of FIG. 1, comprising 2θ angle values of about 7.60; 8.30; 9.55; 11.00; and 12.40.

The Relative Intensity (%) of the mentioned characteristics reflection peaks of Form b at the 2θ angle values are reported in TABLE I.

TABLE I

Angle ($^{\circ}2\theta$)	Relative Intensity (%)
7.60	47.9
8.30	33.4
9.55	36.9
11.00	100.0
12.40	88.1

Form b was characterized with a principal reflection peak
5 at 11.0 deg (2θ).

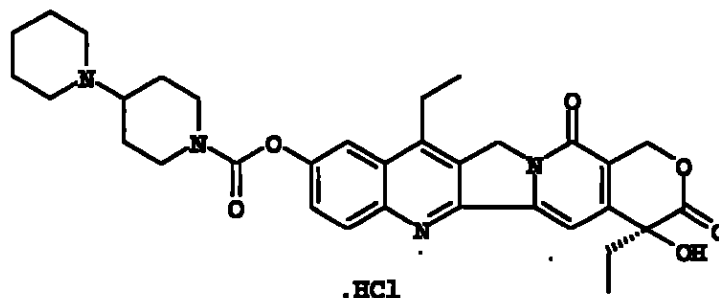
Polymorphism is the property of some molecules to
adopt more than one crystalline form in the solid state. A
single molecule can give rise to a variety of solids having
10 distinct physical properties that can be measured in a
laboratory like its thermal behavior, e.g. melting point
and differential scanning calorimetry ("DSC") thermogram,
dissolution rate, flowability, X-ray diffraction pattern,
infrared absorption spectrum and NMR spectrum. The
15 differences in the physical properties of polymorphs result
from the orientation and intermolecular interactions of
adjacent molecules in the bulk solid. Accordingly,
polymorphs are distinct solids sharing the same molecular
formula which can yet have distinct advantageous and/or
20 disadvantageous physical properties compared to other forms
in the polymorph family. One property of a pharmaceutical
compound that can vary depending upon its polymorphic form
is its rate of dissolution in aqueous solvent. The rate of
dissolution can have therapeutic consequences since it can

affect the rate that an orally administered pharmaceutical is delivered to the bloodstream of a patient.

SUMMARY OF THE INVENTION

5 It is an object of the invention to provide a novel polymorphic form of crystalline irinotecan hydrochloride, methods of use of the polymorph, and methods of manufacture of the polymorph. This and other objects of the invention are provided by one or more of the embodiments described
10 below.

One embodiment of the invention provides a polymorphic form of crystalline irinotecan hydrochloride of formula:



The polymorph is characterized by providing an X-ray powder
15 diffraction pattern comprising 2θ angle values of about 9.15; 10.00; 11.80; 12.20; 13.00 and 13.40. The polymorph can further provide an infrared spectrum containing peaks at 1757, 1712 and 1667 cm⁻¹. The polymorph can provide an X-ray powder diffraction pattern substantially in
20 accordance with that shown in FIG. 2.

Another embodiment of the invention provides a process for preparing the polymorph. The method comprises stirring for a time ranging from about 2 to 48 hours a slurry of irinotecan hydrochloride as Form b or as amorphous, in
25 acetonitrile or in acetone.

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Still another embodiment of the invention provides a pharmaceutical composition that comprises a therapeutically effective amount of the polymorph as an active ingredient and a pharmaceutically acceptable excipient. The pharmaceutical composition can be suitable for injectable administration, oral administration and can be provided in an aqueous dosage form.

Yet another embodiment of the invention provides a method for the preparation of a pharmaceutical composition of irinotecan hydrochloride. The method comprises admixing a therapeutically effective amount of the polymorph of the invention with a pharmaceutically acceptable excipient.

Even another embodiment of the invention provides a method for treating a patient having a cancer. The method comprises administering a therapeutically effective amount of the polymorph. The cancer can be a gastrointestinal such as colorectal cancer.

Another embodiment of the invention provides a method for the preparation of an aqueous solution of irinotecan hydrochloride. The method comprises dissolving the polymorph of the invention into an aqueous solution at room temperature. The aqueous solution can have a pH value ranging from about 3.0 to about 3.8. The final concentration of irinotecan hydrochloride can be higher than about 10 mg/mL.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is illustrated by reference to the accompanying drawings described below.

FIG.1 shows powder X-ray diffractograms of the Form b crystalline polymorph of irinotecan hydrochloride.

FIG.2 shows powder X-ray diffractograms of the Form c crystalline polymorph of irinotecan hydrochloride.

DETAILED DESCRIPTION OF THE INVENTION

It has now been found that irinotecan hydrochloride can exist in another crystalline polymorphic form. This novel crystalline form is fully characterized herein below and is referred to, for convenience, as "Form c".

Owing to its crystalline properties, the new Form c of irinotecan hydrochloride according to the invention has surprising advantages with regard to the crystalline Form b in terms of improved solubility performances.

Solubility enhancement has a significant advantage not only in terms of oral delivery of the active drug substance, but also in terms of improved manufacturability of the parenteral dosage form.

A more soluble and more rapidly dissolving crystal form of an active product ingredient has a significant biopharmaceutical advantage for the oral administration of drugs, being a more prompt dissolution rate behavior of the active drug substance coupled with an improved rate of absorption of the active drug *per se* through the gastrointestinal wall.

In particular, when solubility experimental tests comparing Form c and Form b have been carried out at strong acidic pH 1.2 (this pH value is representative of the environmental pH of the stomach, where the absorption processes through the gastrointestinal wall of acidic moieties starts), it was surprisingly noted that the Form c of irinotecan hydrochloride was 2 orders of magnitude more soluble with respect to the already known Form b (42 mg/mL vs 0.45 mg/mL).

Furthermore, in terms of technological advantages versus the manufacturing of parenteral dosage forms of

irinotecan hydrochloride, the newly found Form c has the advantage of simplifying the current manufacturing procedure.

As stated above, CPT-11 (CAMPTOSAR®) is supplied as a solution formulation where the active drug substance is 20 mg/mL concentrated in solution at a pH value of about 3.5. Being the equilibrium solubility of the Form b at that pH at room temperature lower than 20 mg/mL (its actual value, is in the order of magnitude of about 10 mg/mL), a heating process is needed during the manufacturing to completely solubilize the active at the required concentration. Such heating process generates stable association of Form b molecules in solution (as being known and described in the scientific literature as for example by Aiyama R. et al., Chemical Pharmaceutical Bulletin, 40 (10) 2810-2813), thus increasing also the solubility of the active drug substance at room temperature and allowing the manufacturing of physically stable ready to use 20 mg/mL solution formulations of Form b.

It has now been surprisingly found that the same formulation, with the same quality and long term physical stability, can be prepared with the newly synthesized Form c by simply dissolving the active drug substance in the selected diluent vehicle, thus avoiding any heating step. This fact allows a significant simplification of the manufacturing procedure of the final dosage form, both in terms of manufacturing time and manufacturing process itself. Manufacture the formulation at room temperature is likely dependent on the ability of the molecules of the new Form c to self associate in solution already at room temperature.

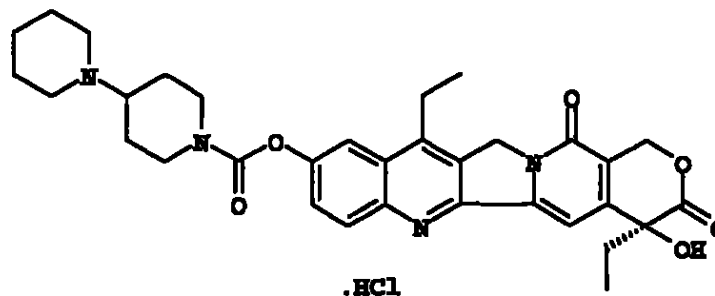
It is therefore another object of the present invention to use Form c for the preparation of an aqueous solution of irinotecan hydrochloride. In particular, the use of Form c is suitable for the preparation of an aqueous solution of irinotecan hydrochloride having a pH value ranging from about 3.0 to about 3.8. More particularly, Form c is suitable for the preparation of an aqueous solution having a pH value ranging from about 3.0 to 3.8 of irinotecan hydrochloride at a concentration higher than about 10 mg/mL.

In a further aspect, the present invention provides a method for the preparation of an aqueous solution of irinotecan hydrochloride, which comprises dissolving the required amount of Form c into an aqueous solution having a pH value ranging from about 3.0 to about 3.8 at room temperature.

No prior art of which applicants are aware describes Form c as now provided herein. To the best of applicants' knowledge, Form c of the invention is previously unknown and are not suggested by the art.

It is therefore an object of the present invention to provide a new crystalline form of irinotecan hydrochloride, which is referred to as Form c.

One embodiment the present invention provides the Form c of crystalline irinotecan hydrochloride of formula:



characterized by providing an X-ray powder diffraction pattern comprising 2 θ angle values of about 9.15; about 10.00; about 11.80; about 12.20; about 13.00 and about 13.40. The relative intensity (%) of the characteristics
5 reflection peaks of Form c at the 2 θ angle values are reported in TABLE II.

TABLE II

Angle ($^{\circ}2\theta$)	Relative Intensity (%)
9.15	100.0
10.00	72.6
11.80	51.6
12.20	21.8
13.00	31.5
13.40	22.6

10 Form c was characterized with a principal reflection peak (100% of relative intensity) at 9.15 deg (2θ).

In particular, the Form c polymorph is characterized by an X-ray powder diffraction spectrum substantially in accordance with that shown in FIG. 2.

15 In a further embodiment, Form c is characterized by an infrared absorption spectrum comprising the following peaks (KBr) ν : 1757(lactone carbonyl), 1712 (carbamate carbonyl) and 1667(pyridone carbonyl) cm^{-1} .

Form b and Form c polymorphs of irinotecan
20 hydrochloride can be readily distinguished by X-ray powder diffraction and infrared absorption spectra.

The relative intensities of the X-ray powder diffraction peaks can vary, depending upon the sample preparation technique, the sample mounting procedure and

the particular instrument employed. Moreover, instrument variation and other factors can affect the 2θ values, therefore, the peak assignments can vary by plus or minus 0.2.

5 The regions of the diffractograms that are most useful in distinguishing the Form b and Form c polymorphs occurs in the region of about 7.00° and 14.00° , wherein all the mentioned characteristic peaks of the two forms are enclosed. For example, the Form c polymorph exhibits a
10 strong peak at 9.15° , while the diffractogram of the Form b polymorph is substantially flat in this region, whilst Form b polymorph exhibits a strong peak at 11.00° , while the diffractogram of the Form c polymorph is substantially flat in this region.

15 Analysis by infrared (IR) is also an useful procedure for polymorphic characterization of crystalline irinotecan hydrochloride, which allows confirmation of the existence of the two polymorphic forms: Form b and Form c, through the detection of three different infra red absorption
20 peaks, as displayed in the following Table III.

TABLE III

	Characteristic Infrared absorption peaks		
	Lactone Carbonyl group	Carbamate Carbonyl group	Pyridone Carbonyl group
Form b	1747	1687	1662
Form c	1757	1712	1667

Water solubility of Form c is more than about 40mg/mL at room temperature.

5 The invention also provides a process for preparing the above Form c, which comprises stirring for a few hours, namely for a time ranging from about 2 to 48 hours, preferably from about 12 to 24 hours, a slurry of irinotecan hydrochloride (as Form b or as amorphous) in
10 acetonitrile or in acetone. The starting materials for preparing Form c, can be obtained by a variety of procedures well known to those of ordinary skill in the art. For example, irinotecan hydrochloride as Form b or as amorphous can be prepared by the general procedure taught
15 by Henegar K. E. et al., J. Org. Chem., 1997, 62, 6588-6597.

Owing to its crystalline properties, Form c of irinotecan hydrochlorid possesses greater solubility than the previously known form, which makes Form c not only more
20 suitable for injectable dosage forms, but also for oral dosage forms with optimal delivery rate in the patient's bloodstream.

In fact the solubility of Form c versus Form b measured in the same experimental conditions (this means at

room temperature at different pHs) is from 4 times (42 mg/mL vs 11 mg/mL in water) to 100 times higher (42.5 mg/mL vs 0.45 mg/mL at pH 1.2). In particular, the solubility of the Form c is 5 times higher at room temperature in the buffering system (lactic acid buffer) currently used in the manufacturing process of the sterile injectable formulation known and marketed as CAMPTOSAR® INJECTION (54.4 mg/mL vs 10 mg/mL).

It is therefore a further object of the present invention to provide a pharmaceutical composition, which comprises a therapeutically effective amount of a polymorphic Form c of irinotecan hydrochloride as an active ingredient and a pharmaceutically acceptable excipient.

It is still another object of the present invention to provide a method for the preparation of a pharmaceutical composition of irinotecan hydrochloride, which comprises admixing a therapeutically effective amount of Form c with a pharmaceutically acceptable excipient.

Pharmaceutical compositions according to the invention can be prepared, for example, as parenteral, oral, transdermal, nasal or pulmonary dosage forms.

Compositions of the invention containing pharmaceutically acceptable excipients can be prepared by any of the well known techniques of pharmacy that comprise admixing the excipients with a drug or therapeutic agent.

For example, Form c may be formulated as an aqueous sterile solution for injectable administration purposes.

The pharmaceutical compositions according to the invention are useful for the prevention, amelioration, and/or treatment of benign and malignant tumors/neoplasias including cancer, such as, for example, brain cancer, bone

20
cancer, epithelial cell-derived neoplasia (epithelial carcinoma) such as basal cell carcinoma, adenocarcinoma, esophageal cancer, small bowel cancer and stomach cancer, colon cancer, liver cancer, bladder cancer, pancreas
5 cancer, ovary cancer, cervical cancer, lung cancers, breast cancer and skin cancer, prostate cancer, renal cell carcinoma, and other known cancers that effect epithelial cells throughout the body. Cancers for which compositions of the invention are contemplated to be particularly useful
10 are gastrointestinal cancers, especially colorectal cancer, lung cancers, especially small cells lung cancer, cervical and pancreatic cancers.

Further disclosed is a method for treating a patient having a cancer, especially a colorectal cancer, which
15 comprises administering a therapeutically effective amount of Form c according to the invention.

It is understood that the specific dose of a compound administered according to this invention to obtain a therapeutic effect will, of course, be determined by the
20 particular circumstances surrounding the administration, including, for example, the age, weight, condition of the patient and administration route; specific dosage regimens can be fit to any particular subject on the basis of the individual need and the professional judgment of the person
25 administering or supervising the administration of the aforesaid compounds.

The dosage range adopted will depend on the route of administration and on the age, weight and condition of the patient being treated. As an example, daily doses of the
30 compounds of the invention, typically administered by parenteral route, for example, intravenously by bolus or infusion is from 1 to 1000 mg/m² body surface area, for

instance from 10 to 500 mg/m². The dosages can be administered at once or can be divided into a number of smaller doses to be administered at varying intervals. A particular example of suitable schedule for parenteral administration of Form c is a 6-week dosing schedule of 125 mg/m² given i.v. over 90 minute of infusion on the first day of weeks 1-4. In another treatment regimen a dose of 350 mg/m² of Form c may be given i.v. over 90 minutes, every third week.

The term "treating" as used herein, unless otherwise indicated, means reversing, alleviating, ameliorating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, refers to the act of treating, as "treating" is defined immediately above.

ANALYTICAL METHODS

X-Ray Powder Diffraction

X-ray powder diffraction data were obtained with a Siemens D500 apparatus, irradiating powder samples with a CuK α graphite-monochromatic (40 kV 40 mA) source between 5° and 35° of 2 θ angle at room temperature. The scan was made of 0.05° steps and the count time was 7 seconds per step.

Infrared absorption

The infrared absorption spectra were obtained using on a Perkin-Elmer FT-IR PARAGON 1000 spectrometer at 4,0 cm⁻¹ resolution. Data were digitised at 2 cm⁻¹ intervals.

The following examples illustrate but do not limit the scope of the invention. All cited references are herein incorporated by reference in their entirety.

EXAMPLES**Example 1****Preparation of irinotecan hydrochloride (Form c)**

10.0 g of irinotecan·HCl·3H₂O Form b were suspended in
5 200 ml of acetone at room temperature.

The mixture was stirred for 24 hours at room temperature and then filtered. The product was dried in vacuo at 45°C for 18 hours and then placed in a chamber in presence of humidity for 24 hours. 9.4 g of Form c was
10 obtained.

Example 2**Preparation of irinotecan hydrochloride (Form c)**

10.0 g of irinotecan·HCl·3H₂O Form b were suspended
15 in 150 ml of acetonitrile at room temperature.

The mixture was stirred for 48 hours at room temperature and then filtered. The product was dried in vacuo at 45°C for 18 hours and then placed in a chamber in presence of humidity for 4 hours. 9.1 g of Form c was
20 obtained.

Example 3**Preparation of irinotecan hydrochloride (Form c)**

10.0 g of irinotecan·HCl amorphous were suspended in
25 200 ml of acetone at room temperature.

The mixture was stirred for 24 hours at room temperature and then filtered. The product was dried in vacuo at 45°C for 18 hours and then placed in a chamber in presence of humidity for 3 hours. 10.0 g of Form c was
30 obtained.

Example 4**Preparation of irinotecan hydrochloride (Form c)**

10.0 g of irinotecan·HCl amorphous were suspended in 250 ml of acetonitrile at room temperature.

5 The mixture was stirred for 48 hours at room temperature and then filtered. The product was dried in vacuo at 45°C for 24 hours and then placed in a chamber in presence of humidity for 5 hours. 8.8 g of Form c was obtained.

10

Example 5**Solubility determination of irinotecan hydrochloride Form c in comparison with Form b**

15 Solubility determination of irinotecan hydrochloride Form c in comparison with Form b has been carried out in the following dissolution media: a) deionized water; b) pH 1.2 buffer (2 g NaCl + 7 mL HCl 37% w/w to 1 Liter); c) Lactate buffer pH 3.5 (this is the formulation currently used for the manufacturing of the parenteral dosage form; 45 mg/ml D-Sorbitol 0.9 mg/ml Lactic Acid in water at pH 3.5. The pH is adjusted to the final value with NaOH 1N). An excess solid was put in glass flasks in the presence of the appropriate dissolution media and the suspensions were shaken at room temperature for 24 hours. Samples were
25 withdrawn after 15, 30, 45, 60 min and 24 hours, filtered and analyzed by means of HPLC assay.

The results are summarized in the following Table IV.

TABLE IV

Time	Irinotecan hydrochloride concentration (mg/ml)					
	Form b			Form c		
	a	b	c	a	b	c
15 MIN	11.03	0.45	10.27	42.04	42.53	54.45
30 MIN	12.10	0.42	10.38	41.50	42.05	55.23
60 MIN	12.12	0.44	10.17	40.62	40.68	53.81
120 MIN	11.80	0.40	11.13	41.15	37.95	54.80
24 HOURS	11.15	0.26	11.06	35.05	0.70	41.95

a = deionized water; b = pH 1.2 buffer; c = lactic acid pH 3.5

The above-tabulated data provide evidence of the improved solubility of Form c when compared with the known Form b.

Example 6

An Injectable Solution of Form c comprises, for example, Injectable solution of Form c

- 1 ml of injectable solution contains:
- 20 mg of Form c (as salt equivalent);
- 45 mg of sorbitol powder; and
- 0.9 mg of lactic acid.

The pH of the solution is adjusted to 3.5 (range, 3.0 to 3.8) with sodium hydroxide or hydrochloric acid.

An injectable solution is available in, for example, single-dose amber glass vials in the following package sizes: 2 mL or 5 mL. This is packaged in a backing/plastic blister to protect against inadvertent breakage and leakage.

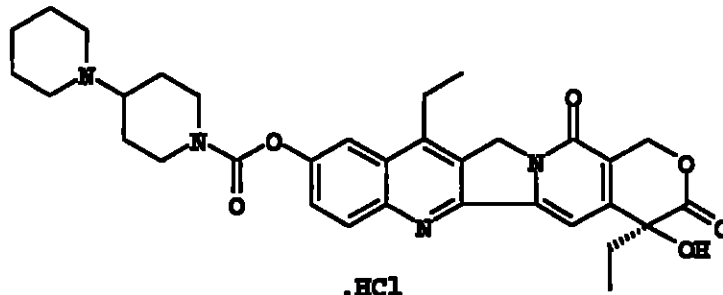
The injectable solution of Form c is intended for dilution with 5% dextrose injection, or 0.9% sodium chloride injection, prior to intravenous infusion. The

preferred diluent is 5% dextrose injection. All the manufacturing procedure have been carried on at room temperature.

The present disclosure is an exemplification of the principles of the invention and is not intended to limit the invention to the particular embodiments illustrated. Those skilled in the art may recognize other equivalents to the specific embodiment described herein which equivalents are intended to be encompassed by the claims attached hereto.

CLAIMS

1. A polymorphic form of crystalline irinotecan hydrochloride of formula:



5 characterized by providing an X-ray powder diffraction pattern comprising 2θ angle values of about 9.15; about 10.00; about 11.80; about 12.20; about 13.00 and about 13.40.

10 2. The polymorph of claim 1, which provides an infrared spectrum containing peaks at 1757, 1712 and 1667 cm⁻¹.

3. The polymorph of claim 1 which provides an X-ray powder diffraction pattern substantially in accordance with
15 that shown in FIG. 2.

4. The polymorph of claim 2 which provides an X-ray powder diffraction pattern substantially in accordance with that shown in FIG. 2.

20

5. A process for preparing the polymorph of claim 1, which comprises stirring for a time ranging from about 2 to 48 hours a slurry of irinotecan hydrochloride as Form b or as amorphous, in acetonitrile or in acetone.

25

27
27

6. A pharmaceutical composition that comprises a therapeutically effective amount of the polymorph of claim 1 as an active ingredient and a pharmaceutically acceptable excipient.

5

7. The composition of claim 6, wherein the composition is suitable for injectable administration.

8. The composition of claim 6, wherein the composition is
10 suitable for oral administration.

9. The composition of claim 6, wherein the composition is in an aqueous dosage form.

15 10. A method for the preparation of a pharmaceutical composition of irinotecan hydrochloride, which comprises admixing a therapeutically effective amount of the polymorph of claim 1 with a pharmaceutically acceptable excipient.

20

11. A method for treating a patient having a cancer, which comprises administering a therapeutically effective amount of a polymorph of claim 1.

25 12. The method of claim 11, wherein the cancer is a gastrointestinal cancer.

13. The method of claim 12, wherein the gastrointestinal cancer is a colorectal cancer.

30

14. A method for treating a patient having a cancer, which comprises administering the pharmaceutical composition of claim 6.

5 15. The method of claim 14, wherein the cancer is a gastrointestinal cancer.

16. The method of claim 15, wherein the gastrointestinal cancer is a colorectal cancer.

10

17. A method for the preparation of an aqueous solution of irinotecan hydrochloride, that comprises dissolving the polymorph of claim 1 into an aqueous solution at room temperature.

15

18. The method of claim 17, wherein the aqueous solution has a pH value ranging from about 3.0 to about 3.8.

19. The method of claim 18, wherein the final
20 concentration of irinotecan hydrochloride is higher than about 10 mg/mL.

FIGURE 1

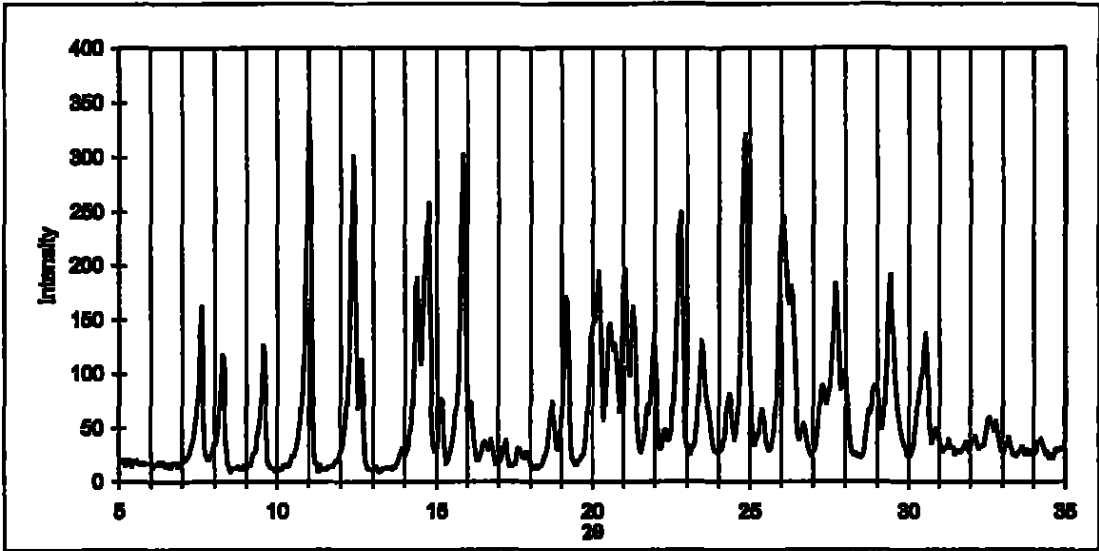
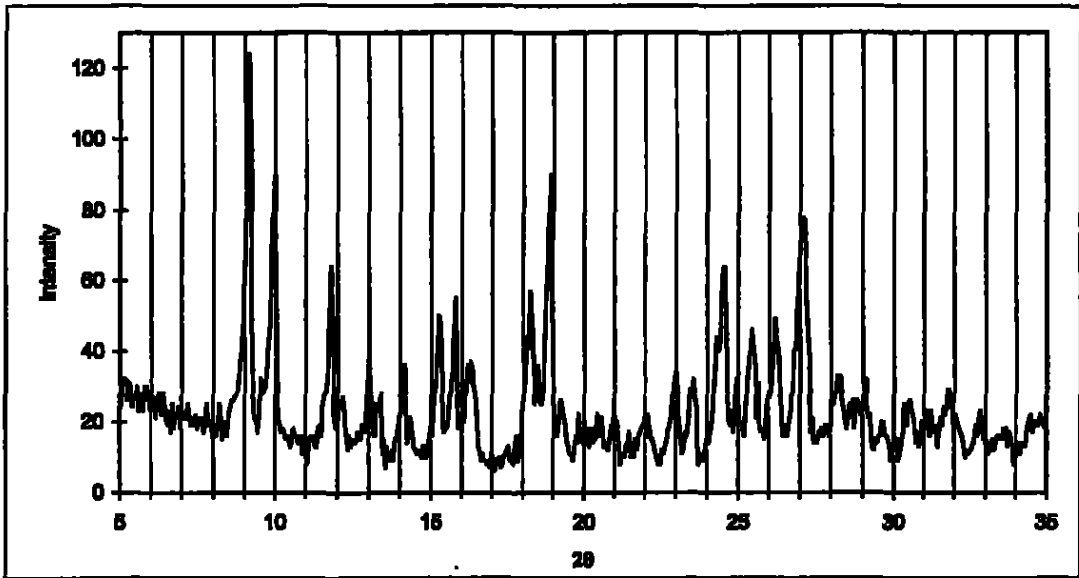


FIGURE 2



INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/01948

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D491/22 A61K31/4375 A61P35/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

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

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

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SAWADA S ET AL: "SYNTHESIS AND ANTITUMOR ACTIVITY OF 20(S)-CAMPTOTHECIN DERIVATIVES: CARBAMATE-LINKED, WATER-SOLUBLE DERIVATIVES OF 7-ETHYL-10-HYDROXYCAMPTOTHECIN" CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN. TOKYO, JP, vol. 39, no. 6, 1 June 1991 (1991-06-01), pages 1446-1454, XP000653715 ISSN: 0009-2363 cited in the application Preparation of 6-27, mp=222-223°C, IR: 1747, 1715, 1655 — -/-	1-19

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

☐ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claims or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document relating to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "Z" document member of the same patent family

Date of the actual completion of the international search

10 July 2003

Date of mailing of the international search report

18/07/2003

Name and mailing address of the ISA

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Authorized officer

Diederix, J

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/01948

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HENEGAR K E ET AL: "PRACTICAL ASYMMETRIC SYNTHESIS OF (S)-4-ETHYL-7,8-DIHYDRO-4-HYDROXY-1H-PYRANOL3,4-F INDOLIZINE-3,6,10(4H)-TRIONE, A KEY INTERMEDIATE FOR THE SYNTHESIS OF IRINOTECAN AND OTHER CAMPTOTHECIN ANALOGS" JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, US, vol. 62, no. 19, 1997, pages 6588-6597, XP002935575 ISSN: 0022-3263 cited in the application Preparation of Irinotecan: mp=259-260°C	1-19

32

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/01948

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

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

- ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 11-16 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
- ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
- ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

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

Remark on Protest

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

FÓRMULA POLIMÓRFICA CRISTALINA DE
CLORHIDRATO DE IRINOTECAN

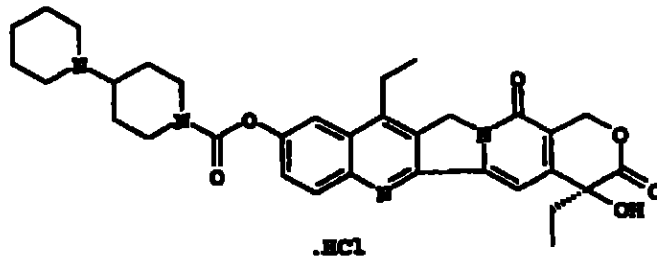
RESUMEN DE LA INVENCIÓN

Esta invención se relaciona con una forma polimórfica cristalina novedosa del compuesto clorhidrato de (S)-4,11-Dietil-3,4,12,14-tetrahidro-4-hidroxi-3,14-dioxo-1H-pirano[3',4':6,7]indolizino[1,2-b]-quinolin-9-il [1,4'-bipiperidina]-1'-carboxilato (irinotecan). Un proceso para preparar esta forma polimórfica novedosa, composiciones farmacéuticas que la comprenden como un ingrediente activo y el uso del mismo y sus composiciones farmacéuticas como un agente terapéutico también están dentro del alcance de la presente invención.

ANTECEDENTES DE LA INVENCIÓN

El clorhidrato de irinotecan, el compuesto clorhidrato de (S)-4,11-Dietil-3,4,12,14-tetrahidro-4-hidroxi-3,14-dioxo-1H-pirano[3',4':6,7]indolizino[1,2-b]-quinolin-9-il [1,4'-bipiperidina]-1'-carboxilato que tiene la fórmula

34



Es un análogo de camptotecina y un inhibidor de topoisomerasa 1 derivado del compuesto de ocurrencia natural en el árbol chino *Camptotheca acuminata*.

Desde su aprobación en los estados unidos en 1996, el trihidrato de clorhidrato de irinotecan (CPT-11, CAMPTOSAR®, inyección, Pharmacia Corp.; Peapack NetworkJustice) ha sufrido una extensa evaluación clínica. En los pasados cinco años, el centro de desarrollo ha evolucionado desde la evaluación de la actividad del agente simple en escenarios de enfermedad refractaria para evaluación de regímenes de quimioterapia de combinación basados en irinotecan de "front-line" y la integración de irinotecan en regímenes de modalidad combinada. Estudios importantes se han desarrollado que clarifican el papel del irinotecan que trata cánceres colorectales y otros cánceres gastrointestinales, cáncer

35

de pulmón de célula pequeña y no celulares, y una variedad de otras malignidades.

El CPT-11 ha mostrado una actividad contra una variedad de tipos de tumor, particularmente tumores colorectales refractarios, y se utiliza para el tratamiento de varias formas de cáncer. Su uso primario es en el tratamiento de cáncer de colón, particularmente cáncer de colon avanzado. También es de interés para el tratamiento de otros cánceres, tales como cánceres de pulmón, el estómago y el páncreas.

El CPT-11 es usualmente administrado en uno de dos regímenes de tratamiento. En un régimen, una dosis de 125 mg/m² de CPT es dada i.v. durante un periodo de 90 minutos cada semana durante cuatro semanas. Después de un lapso de dos semanas esto se repite, de tal forma que el paciente recibe CPT-11 durante cuatro semanas de cada 6. En otro régimen de tratamiento le es dada una dosis de 350 mg/m² i.v. durante 90 minutos, cada tercer semana. Así, un régimen opera con un ciclo de seis semanas y el otro régimen en un ciclo de tres semanas.

36

El CPT-11 se indica como un componente de terapia de primera línea en combinación con 5-FU/LV para el tratamiento de pacientes con carcinoma metastásico del colon o recto. El CPT-11 también se indica para pacientes con carcinoma metastásico del colon o el recto cuya enfermedad ha recurrido o progresado luego de la terapia inicial basada en 5-FU. El CPT-11 es el primer inhibidor de topoisomerasa I con actividad conocida y cáncer colorectal, y el primer tratamiento de cáncer colorectal completamente probado por la FDA en cuarenta años.

La actividad antitumoral del CPT-11 se atribuye a un metabolito activo, la 7-etil-10-hidroxi 20(S)camptotecina (SN-38), que es producida después de clivaje enzimático por carboxilesterasas en el hígado, intestino delgado y plasma. El SN-38 es 100 veces más citotóxico que el CPT-11.

El CPT-11 (CAMPTOSAR®) se suministrado como una solución estéril, amarillo pálido, clara, acuosa. Esta está disponible en dos tamaños de dosis simple: frascos llenos con 2 ml contienen 40 mg de clorhidrato de irinotecan y frascos llenos con 5 ml contienen 100 mg de clorhidrato de irinotecan. Cada mililitro de solución contiene 20 mg

de clorhidrato de irinotecan (sobre la base de una sal trihidratada), 45 mg de polvo de sorbitol, y 0,9 mg de ácido láctico. El pH de la solución se ha ajustado a 3,5 (rango, 3,0 a 3,8) con hidróxido de sodio o ácido clorhídrico. El CAMPTOSAR® está destinado a dilución con inyección de dextrosa al 5% (D5W), o inyección de clorhidrato de sodio al 0,9%, antes de infusión intravenosa. El diluyente preferido es una inyección de dextrosa al 5%. La patente estadounidense de Yakult No. 4,604,463 describe una amplia familia de derivados de camptotecina que incluye irinotecan, sus sales farmacéuticamente aceptables y la preparación de estas.

La patente estadounidense de Pharmacia y Upjohn Co. No. 6,121,451 describe intermedios y procesos para la síntesis de derivados de camptotecina tales como clorhidrato de irinotecan.

La solicitud de patente internacional de Pharmacia y Upjohn S.p.A. No. WO 01/10443 y WO 01/30351 describe preparaciones farmacéuticas orales que comprenden clorhidrato de irinotecan.

Sawada et al., Chem. Pharm. Bull. Vol. 39, No. 6, 1446-54 (1991), describe la preparación de irinotecan de camptotecina natural en cinco etapas químicas y 20% de rendimientos totales. Sawada además describe la estructura de cristal del trihidrato de clorhidrato de irinotecan (también conocida como CPT-11 que es aquella que es habitualmente utilizada para la elaboración del producto comercialmente disponible), como agujas amarillas ligeramente pálidas o polvo cristalino mediante cristalización de agua. El producto es luego secado (in vacuo) y equilibrado en una cámara de humedad relativa 75% durante 70 horas. La forma cristalina del trihidrato de clorhidrato de irinotecan como se describió por Sawada et al. es aquí después denominada como, por conveniencia, "Forma b".

Un resumen de las propiedades físicas de la forma b son reportadas adelante.

Absorción Infrarroja

IR (KBr) ν : 1748 (carbonil lactona), 1688 (carbonil carbamato), 1663 (carbonilpiridona), cm^{-1} .

21
29**Solubilidad en Agua**

La solubilidad en agua de la forma b es a temperatura ambiente de cuarto de aproximadamente 10 mg/mL.

Difracción con polvo por rayos X (PXRD)

La Forma b también se caracterizó por su patrón de difracción con polvo de rayos x, como se mostró en el espectro de la figura 1, que comprende valores de ángulo 2θ de aproximadamente 7,60; 8,30; 9,55; 11,00; y 12,40.

La Intensidad Relativa (%) de los picos de reflexión características mencionados de la Forma b en los valores de ángulo 2θ se reportan en la TABLA I.

TABLA I

Ángulo ($^{\circ}2\theta$)	Intensidad Relativa (%)
7,60	47,9
8,30	33,4
9,55	36,9
11,00	100,0
12,40	88,1

40
43

La Forma b se caracterizó por un pico de reflexión principal en 11,0 grados (2 θ).

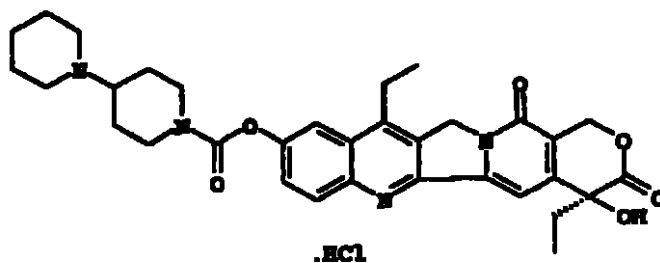
El polimorfismo es la propiedad de algunas moléculas de adaptar más de una forma cristalina en el estado sólido. Una molécula simple puede dar origen a una variedad de sólidos que tienen propiedades físicas distantes que se pueden medir en un laboratorio como su comportamiento térmico, por ejemplo, punto de fusión y termograma de calorimetría de exploración diferencial ("DSC"), índice de disolución, fluibilidad, patrón de difracción de rayos X; espectro de absorción infrarrojo y espectro RMN. Las diferencias en las propiedades físicas del polimorfo resultan de la orientación y las interacciones intermoleculares de las moléculas adyacentes en el sólido en masa. De acuerdo con esto, los polimorfos son sólidos diferentes que comparen la misma fórmula molecular que pueden tener aún ventajas diferentes y/o propiedades físicas desventajosas comparadas con otras formas en la familia del polimorfo. Una propiedad de un compuesto farmacéutico que puede variar dependiendo de su forma polimórfica es su índice de disolución en solvente

acuoso. El índice de disolución puede tener consecuencias terapéuticas en razón a que este puede afectar el índice que es suministrado a un fármaco administrado oralmente al torrente sanguíneo de un paciente.

RESUMEN DE LA INVENCION

Es un objeto de la invención suministrar una forma polimórfica novedosa de clorhidrato de irinotecan cristalino, métodos de uso del polimorfo, y métodos de elaboración del polimorfo. Este y otros objetos de la invención se suministran como una o más de las modalidades descritas adelante.

Una modalidad de la invención suministra una forma polimórfica de clorhidrato de irinotecan cristalino de fórmula:



42

El polimorfo se caracteriza por suministrar un patrón de difracción con polvo por rayos X que comprende valores de ángulo 2θ de aproximadamente 9,15; 10,00; 12,80; 12,20; 13,00 y 13,40. El polimorfo puede además suministrar un espectro infrarrojo que contiene picos en 17,57, 17,12 y 16,67 cm^{-1} . El polimorfo puede suministrar un patrón de difracción en polvo por rayos X sustancialmente de acuerdo con aquel que se muestra en la figura 2.

Otra modalidad de la invención suministra un proceso para preparar el polimorfo. El método comprende agitar durante un tiempo que varía desde aproximadamente 2 a 48 horas una lechada de clorhidrato de irinotecan como Forma b o como amorfo, en cetónitrilo o en acetona.

Aún otra modalidad de la invención suministra una composición farmacéutica que comprende una cantidad terapéuticamente efectiva del polimorfo como un ingrediente activo y un excipiente farmacéuticamente aceptable. La composición farmacéutica puede ser adecuada para administración inyectable, administración oral y se puede suministrar en una forma de dosis acuosa.

43

Aún otra modalidad de la invención suministra un método para la preparación de una composición farmacéutica de clorhidrato de irinotecan. El método comprende mezclar una cantidad terapéuticamente efectiva del polimorfo de la invención con un excipiente farmacéuticamente aceptable.

Aún otra modalidad de la invención suministra un método para tratar un paciente que tiene cáncer. El método comprende administrar una cantidad terapéuticamente efectiva del polimorfo. El cáncer puede ser un cáncer gastrointestinal tal como el colorectal.

Otra modalidad de la invención suministra un método para la preparación de una solución acuosa de clorhidrato de irinotecan. El método comprende disolver el polimorfo de la invención en una solución acuosa a temperatura ambiente de cuarto. La solución acuosa puede tener un valor de pH que varía desde 3,0 a aproximadamente 3,8. La concentración final de clorhidrato de irinotecan puede mayor de aproximadamente 10 mg/mL.

LH
LH**BREVE DESCRIPCIÓN DE LOS DIBUJOS**

La invención se ilustra mediante referencia a los dibujos que la acompañan descritos adelante.

La figura 1 muestra difractogramas con polvo por rayos X de la Forma b del polimorfo cristalino de clorhidrato de irinotecan.

La figura 2 muestra difractogramas con polvo por rayos X de la Forma c del polimorfo cristalino de clorhidrato de irinotecan.

DESCRIPCIÓN DETALLADA DE LA INVENCION

Se ha encontrado ahora que el clorhidrato de irinotecan puede existir en otra forma polimórfica cristalina. Esta forma cristalina novedosa se caracteriza completamente aquí adelante y es denominada como, por conveniencia, "Forma c".

Debido a sus propiedades cristalinas, la nueva Forma c del clorhidrato de irinotecan de acuerdo con la invención tiene ventajas sorprendentes con relación a la Forma b

cristalina en términos de desempeño de solubilidad mejorada.

El mejoramiento de la solubilidad tiene una ventaja significativa no solamente en términos de suministro oral de la sustancia de droga activa, sino también en términos de la manufacturabilidad mejorada de la forma de dosis parenteral.

Una forma cristalina de solubilidad y disolución más rápida de un ingrediente de producto activo tiene una ventaja biofarmacéutica significativa para la administración de la droga, siendo un comportamiento con índice de disolución más rápido de la sustancia de droga activa acoplada con un índice mejorado de absorción de la droga activa per se a través de la pared gastrointestinal.

En particular, cuando ensayos experimentales de solubilidad que comparan la Forma c y la Forma b se han llevado a cabo a pH ácidos fuertes de 1,2 (este valor de pH es representativo del pH ambiental del estómago, donde inician los procesos de absorción a través de la pared gastrointestinal de las porciones ácidas), fue

sorprendentemente notorio que la Forma c del clorhidrato de irinotecan era dos órdenes de magnitud más soluble con respecto a la Forma b ya conocida (42 mg/mL Vs 0,45 mL).

Adicionalmente, en términos de ventajas tecnológicas contra la elaboración de formas de dosis parenteral de clorhidrato de irinotecan, la Forma c encontrada tiene la ventaja de simplificar el procedimiento de elaboración actual.

Como es estableció anteriormente, el CPT-11 (CAMPTOSAR®) es suministrado como una formulación en solución en donde la sustancia de la droga activa es 20 mg/mL concentrada en solución a un pH de cerca de 3,5. Siendo la solubilidad de equilibrio en la Forma b en aquel pH a temperatura ambiente inferior a 20 mg/mL (su valor actual, está en el orden de magnitud de cerca de 10 mg/mL), un proceso de calentamiento es necesario durante la fabricación para solubilizar completamente el activo a la concentración requerida. Tal proceso de calentamiento genera una asociación estable de las moléculas de la Forma b en solución (como es conocido y descrito en la literatura científica como por ejemplo por Aiyama R. et al., Chemical Pharmacuetical Bulletin, 40 (10) 2810-

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2813), incrementando así también la solubilidad de la sustancia de la droga activa a temperatura ambiente y permitiendo la fabricación de las formulaciones de solución de Forma b físicamente estables y listas para usar de 20 ml/mL.

Se ha encontrado de manera sorprendente que la misma formulación, con la misma calidad y estabilidad física a largo término, puede ser preparada con la Forma c recientemente sintetizada por medio de simplemente disolver la sustancia de la droga activa en el vehículo diluyente seleccionado, evitando cualquier etapa de calentamiento. Este hecho permite una simplificación significativa del procedimiento de fabricación de la forma de dosificación final, tanto en términos de tiempo de fabricación como del proceso de fabricación mismo. La fabricación de la formulación a temperatura ambiente es dependiente similarmente de la habilidad de las moléculas de la nueva Forma c para asociarse a si mismas en una solución ya a temperatura ambiente.

Es por lo tanto otro objeto de la presente invención usar la Forma c para la preparación de una solución acuosa de clorhidrato de irinotecan. En particular, el uso de la

Forma c es adecuado para la preparación de una solución acuosa de clorhidrato de irinotecan que tiene un valor de pH que varía entre cerca de 3,0 acerca de 3,8. Más particularmente, la Forma c es adecuada para la preparación de una solución acuosa que tiene un valor pH que varía entre cerca de 3,0 a 3,8 de clorhidrato de irinotecan a una concentración mayor de cerca de 10 mg/mL.

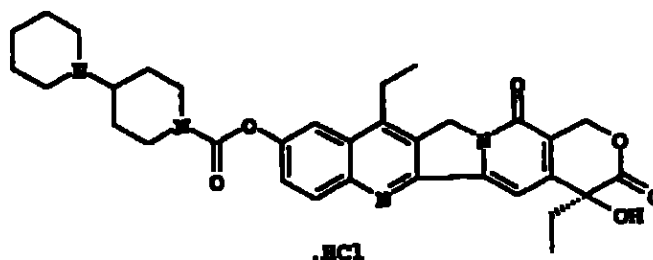
En un aspecto adicional, la presente invención suministra un método para la preparación de una solución acuosa de clorhidrato de irinotecan, que comprende disolver la cantidad requerida de la Forma c en una solución acuosa que tiene un valor de pH que varía entre cerca de 3,0 acerca de 3,8 a temperatura ambiente.

Ninguna técnica anterior de la cual los solicitantes tengan conocimiento describe la Forma c como se suministra aquí. De acuerdo con el mejor conocimiento del solicitante, la Forma c de la invención es desconocida en el estado de la técnica y no ha sido sugerida por la técnica.

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Por lo tanto un objeto de la presente invención es suministrar una nueva forma cristalina de clorhidrato de irinotecan, que se refiere aquí como la Forma c.

Una modalidad de la presente invención suministra la Forma c de clorhidrato cristalino de irinotecan de fórmula:



Caracterizada por suministrar un patrón de difracción en polvo por rayos X que comprende valores de ángulo 2θ de cerca de 9,15; cerca de 10,00 cerca de 11,80; cerca de 12,20; cerca de 13,00 y cerca de 13,40. La intensidad relativa (%) de los picos de reflexión característicos de la Forma c a valores de ángulo 2θ se reportan en la tabla II.

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TABLA II

Ángulo ($^{\circ}2\theta$)	Intensidad Relativa (%)
9,15	100,0
10,00	72,6
11,80	51,6
12,20	21,8
13,00	31,5
13,40	22,6

La Forma c se caracterizó con un pico de reflexión principal (100% de intensidad relativa) a $9,15^{\circ}$ (2θ).

En particular el polimorfo de Forma c está caracterizado por un espectro de difracción de polvo por rayos X sustancialmente de acuerdo con lo mostrado en la figura 2.

En una modalidad adicional, la Forma c está caracterizada por un espectro de absorción de infrarrojos que comprende los siguientes picos (KBr) ν : 1757 (lactona carbonilo), 1712 (carbamato carbonilo) y 1667 (piridona carbonilo) cm^{-1} .

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Los polimorfos de Forma b y Forma c del clorhidrato de irinotecan pueden distinguirse fácilmente por la difracción con polvo por rayos X y el espectro de absorción de infrarrojos.

Las intensidades relativas de los picos de difracción en polvo por rayos X pueden variar, dependiendo de la técnica de preparación de la muestra, el procedimiento de montaje de la muestra y el instrumento particular empleado. Más aún, la variación de instrumento y otros factores pueden afectar los valores 2θ , por lo tanto, las asignaciones de pico pueden variar más o menos 0,2.

Las regiones de los difractogramas que son más útiles para distinguir los polimorfos de Forma b y Forma c ocurren en la región entre cerca de $7,00^\circ$ y $14,00^\circ$, en donde todos los picos característicos mencionados de las dos formas están encerrados. Por ejemplo, el polimorfo de Forma c exhibe un pico fuerte en $9,15^\circ$, mientras que el difractograma del polimorfo de Forma b es sustancialmente plano en esta región, mientras que el polimorfo de Forma b exhibe un pico fuerte en $11,00^\circ$, mientras que el

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difractograma del polimorfo de Forma c es sustancialmente plano en esta región.

El análisis por infrarrojo (IR) es también un procedimiento útil para la caracterización polimórfica del clorhidrato de irinotecan cristalino, que permite la confirmación de la existencia de las dos formas polimórficas: la Forma b y la Forma c, por medio de la detección de tres diferentes picos de absorción de infrarrojos como se muestra en la siguiente Tabla III.

TABLA III

Picos característicos de absorción de infrarrojos			
	Grupo lactona carbonilo	Grupo carbamato carbonilo	Grupo piridona carbonilo
Forma b	1474	1687	1662
Forma c	1757	1712	1667

La solubilidad en agua de la Forma c es más de cerca de 40 mg/mL a temperatura ambiente.

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La invención también suministra un proceso para preparar la anterior Forma c, que comprende agitar durante unas pocas horas, particularmente durante un rango de tiempo entre 2 a 48 horas, preferiblemente cerca de 12 a 24 horas, una suspensión de clorhidrato de irinotecan (como Forma b o como amorfo) en acetonitrilo o en acetona. Los materiales de partida para preparar la Forma c, pueden ser obtenidos por una variedad de procedimientos bien conocidos por aquellos versados en la técnica. Por ejemplo, el clorhidrato de irinotecan como Forma b o como amorfo puede ser preparado por el procedimiento general enseñado por Henegar K. E. et al., J. Org. Chem., 1997, 62, 6588-6597.

Debido a sus propiedades cristalinas, la Forma c del clorhidrato de irinotecan posee mayor solubilidad que la forma previamente conocida, lo que hace la Forma c no solamente más adecuada para formas de dosificación inyectables, sino también para formas de dosificación oral con un índice de suministro óptimo en el torrente sanguíneo del paciente.

De hecho la solubilidad de la Forma c contra la Forma b medida en las mismas condiciones experimentales (esto significa a temperatura ambiente y a diferentes pH) es entre 4 veces (42 mg/ml versus 11 mg/mL en agua) a 100 veces mayor (42,5 mg/mL versus 0,45 mg/mL a pH 1,2). En particular, la solubilidad de la Forma c es cinco veces mayor a temperatura ambiente en el sistema de amortiguación (amortiguador de ácido láctico) corrientemente usado en el proceso de fabricación de formulaciones inyectables estériles conocidas y comercializadas como INYECCIÓN CAMPTOSAR® (54,4 mg/mL versus 10 mg/mL).

Por lo tanto es un objetivo adicional de la presente invención suministrar una composición farmacéutica, que comprende una cantidad terapéuticamente efectiva de una Forma c polimórfica de clorhidrato de irinotecan como un ingrediente activo y un excipiente farmacéuticamente aceptable.

Todavía otro objeto de la presente invención es suministrar un método para la preparación de una composición farmacéutica de clorhidrato de irinotecan, que comprende mezclar una cantidad terapéuticamente

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efectiva de la Forma c con un excipiente farmacéuticamente aceptable.

Las composiciones farmacéuticas de acuerdo con la invención pueden ser preparadas, por ejemplo, como formas de dosificación parenteral, oral, transdérmica, nasal o pulmonar.

Las composiciones de la invención que contienen excipientes farmacéuticamente aceptables pueden ser preparadas por cualquiera de las técnicas bien conocidas de farmacia que comprenden mezclar los excipientes con una droga o agente terapéutico.

Por ejemplo, la Forma c puede ser formulada como una solución acuosa estéril para propósitos de administración inyectable.

Las composiciones farmacéuticas de acuerdo con la invención son útiles en la prevención, mejoramiento y/o tratamiento de tumores benignos y malignos/neoplasias incluyendo cáncer tales como, por ejemplo, cáncer de cerebro, cáncer de huesos, neoplasia epitelial derivada de células (carcinoma epitelial) tales como el carcinoma

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de célula basal, adenocarcinoma, cáncer esofágico, cáncer del intestino delgado y cáncer de estómago, cáncer del colon, cáncer de hígado, cáncer del riñón, cáncer de páncreas, cáncer de ovarios, cáncer cervical, cáncer de pulmones, y cáncer de pecho y cáncer de piel, cáncer de próstata, carcinoma de célula renal, y otros cánceres conocidos que afectan las células epiteliales por todo el cuerpo. Los cánceres de los cuales las composiciones de la invención están contempladas para ser particularmente útiles son los cánceres gastrointestinales, especialmente cánceres colorectales, cánceres de pulmón, especialmente cánceres de pulmón de células pequeñas, cánceres cervicales y pancreáticos.

Se describe adicionalmente un método para tratar un paciente que tiene un cáncer, especialmente cáncer colorectal, que comprende administrar una cantidad terapéuticamente efectiva de la Forma c de acuerdo con la invención.

Es entendido que la dosis específica de un compuesto administrado de acuerdo con esta invención para obtener un efecto terapéutico será, por supuesto, determinado por la circunstancias particulares que rodean la

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administración, incluyendo, por ejemplo, la edad, peso, condición del paciente y vía de administración; regímenes de dosificación específicas pueden ajustarse a cualquier sujeto particular sobre la base de la necesidad individual y el juzgamiento profesional de la persona que administra o supervisa la administración de los compuestos anteriormente mencionados.

El rango de dosificación adoptado dependerá de la vía de administración y de la edad, peso y condición del paciente que va a ser tratado. Como un ejemplo, dosis diarias de los compuestos de la invención, típicamente administrados por vía parenteral, por ejemplo, de manera intravenosa por bolo o infusión están entre 1 a 1.000 mg/m² por área de superficie de cuerpo, por ejemplo entre 10 a 500 mg/m². Las dosificaciones pueden ser administradas de una sola vez o pueden ser divididas en un número de dosis más pequeñas para ser administradas a intervalos variables. Un ejemplo particular de un programa adecuado para administración parenteral de la Forma C es un programa de dosificación de 6 semanas de 125 mg/m² i.v. durante 90 minutos de infusión sobre el primer día de las semanas 1 a 4. En otro régimen de

tratamiento una dosis de 350 mg/m² de la Forma c puede ser dada i.v. durante 90 minutos cada tercer semana.

El término "tratamiento" como se usa aquí, a menos que se indique otra cosa, significa invertir, aliviar, mejorar, inhibir el progreso de, o impedir el desorden o condición al cual tal término aplica, o uno o más síntomas de tal desorden o condición. El término "tratamiento", como se usa aquí se refiere al acto de tratar, como "tratar" según se definió inmediatamente antes.

MÉTODOS ANALÍTICOS

Difracción con Polvo por Rayos X

Los datos de la difracción con polvo por rayos X fueron obtenidos con un aparato Siemens D500, que irradia muestras de polvo con CuK α grafito monocromático (40 kV 40 mA) como fuente entre 5° y 35° de ángulo 2 θ a temperatura ambiente. El barrido fue hecho en etapas de 0,05° y el tiempo de cuenta fue de 7 segundos por etapa.

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Absorción Infrarroja

El espectro de absorción de infrarrojos fue obtenido usando un espectrómetro Perkin-Elmer FT-IR PARAGON a una resolución de 4,0 cm^{-1} . Los datos fueron digitalizados a intervalos de 2 cm^{-1} .

Los siguientes ejemplos ilustran pero no limitan el alcance de la invención. Todas las referencias citadas son incorporadas aquí como referencia en su totalidad.

EJEMPLOS

Ejemplo 1

Preparación de clorhidrato de irinotecan (Forma c)

10,0 g de irinotecan·HCl·3H₂O Forma b se suspendieron en 200 ml de acetona a temperatura ambiente.

La mezcla se agitó durante 24 horas a temperatura ambiente y luego se filtró. El producto se secó en vacío a 45° C durante 18 horas y luego colocado en una cámara

en presencia de humedad durante 24 horas. Se obtuvo 9,4 g de Forma c.

Ejemplo 2

Preparación de clorhidrato de irinotecan (Forma c)

10,0 g de irinotecan·HCl·3H₂O Forma b se suspendieron en 150 ml de acetonitrilo a temperatura ambiente.

La mezcla se agitó durante 48 horas a temperatura ambiente y luego se filtró. El producto se secó en vacío a 45° C durante 18 horas y luego colocado en una cámara en presencia de humedad durante 4 horas. Se obtuvo 9,1 g de la Forma c.

Ejemplo 3

Preparación de clorhidrato de irinotecan (Forma c)

10,0 g de irinotecan·HCl amorfo se suspendieron en 200 ml de acetona a temperatura ambiente.

La mezcla se agitó durante 24 horas a temperatura ambiente y luego se filtró. El producto se secó en vacío a 45° C durante 18 horas y luego colocado en una cámara en presencia de humedad durante 3 horas. Se obtuvo 10,0 g de la Forma c.

Ejemplo 4

Preparación de clorhidrato de irinotecan (Forma c)

10,0 g de irinotecan·HCl amorfo se suspendieron en 250 ml de acetonitrilo a temperatura ambiente.

La mezcla se agitó durante 48 horas a temperatura ambiente y luego se filtró. El producto se secó en vacío a 45° C durante 24 horas y luego colocado en una cámara en presencia de humedad durante 5 horas. Se obtuvo 8,8 g de la Forma c.

Ejemplo 5

Determinación de solubilidad de clorhidrato de irinotecan

Forma c en comparación con la Forma b

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La determinación de solubilidad del clorhidrato de irinotecan Forma c en comparación con la Forma b se ha llevado a cabo en el siguiente medio de disolución: a) agua desionizada; b) amortiguador pH 1,2 (2 g NaCl + 7 mL HCl 37% p/p a 1 litro); c) amortiguador de lactato pH 3,5 (esta es la formulación utilizada actualmente para la fabricación de formas de dosis parenteral; D-Sorbitol 45 mg/ml ácido láctico 0,9 mg/ml en agua a un pH de 3,5. El pH se ajusta al valor final con NaOH 1N). Se colocó un exceso de sólidos en frascos de vidrio en la presencia del medio de disolución apropiado y las suspensiones se agitaron a temperatura ambiente durante 24 horas. Las muestras fueron retiradas después de 15, 30, 45, 60 minutos y 24 horas, filtradas y analizadas por medios de ensayos de HPLC.

Los resultados se miden en la siguiente tabla IV.

TABLA IV

Tiempo	Concentración de clorhidrato de irinotecan (mg/ml)					
	Forma b			Forma c		
	a	b	c	a	b	c
15 MIN	11, 03	0, 45	10, 27	42, 04	42, 53	54, 45
30 MIN	12, 10	0, 42	10, 38	41, 50	42, 05	55, 23
60 MIN	12, 12	0, 44	10, 17	40, 62	40, 68	53, 81
120 MIN	11, 80	0, 40	11, 13	41, 15	37, 95	54, 80
24 HORAS	11,15	0,26	11,06	35,05	0,70	41, 95

a = agua desionizada; b = amortiguador pH 1,2; c = ácido láctico pH 3,5

Los anteriores datos tabulados proporcionan evidencia de la solubilidad mejorada de la Forma c comparada con la Forma b conocida.

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Una solución inyectable de la Forma c comprende, por ejemplo, solución inyectable de la Forma c

1 ml de solución inyectable contiene:

20 mg de Forma c (como sal equivalente);

45 mg de polvo de sorbitol; y

0,9 mg de ácido láctico.

El pH de la solución se ajusta a 3,5 (rango, 3,0 a 3,8) con hidróxido de sodio o ácido clorhídrico

Una solución inyectable está disponible en, por ejemplo, frascos de vidrio ámbar de dosis sencilla en los siguientes tamaños de paquete: 2 mL o 5 mL. Este es empacado en una ampolla plástica de respaldo para proteger contra rompimiento y escape involuntario.

La solución inyectable de la Forma C está hecha para dilusión con inyección de dextrosa 5%, o 0,9% de

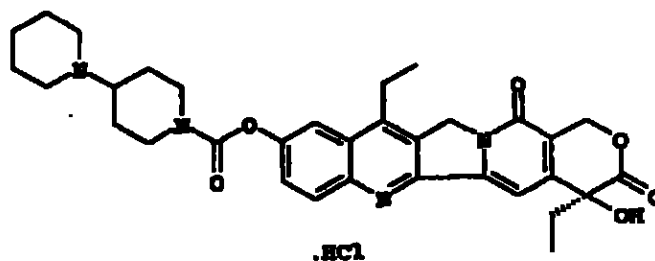
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inyección de cloruro de sodio, antes de infusión intravenosa. El diluyente preferido es 5% de inyección de dextrosa. Todos los procedimientos de fabricación se han llevado a cabo a temperatura ambiente.

La presente descripción es una ejemplificación de los principios de la invención y no pretende limitar la invención a las modalidades ilustradas particulares. Aquellos expertos en la técnica pueden reconocer otras equivalencias a la modalidad descrita aquí cuyos equivalentes se pretenden sean abarcados por las reivindicaciones adjuntas.

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12REIVINDICACIONES

1. Una forma polimórfica de clorhidrato de irinotecan cristalino de fórmula:



- Caracterizado por suministrar un patrón de difracción con polvo por rayos X que comprende valores de ángulo de 2θ de aproximadamente 9,15; aproximadamente 10,00; aproximadamente 11,80; aproximadamente 12,20; aproximadamente 13,00 y aproximadamente 13,40.
2. El polimorfo de la reivindicación 1, que suministra un espectro infrarrojo que contiene picos en 1757, 1712 y 1667 cm^{-1} .

3. El polimorfo de la reivindicación 1 que suministra un patrón de difracción con polvo por rayos X sustancialmente de acuerdo con lo mostrado con en la figura 2.
4. El polimorfo de la reivindicación 2 que suministra un patrón de difracción con polvo por rayos X sustancialmente de acuerdo con lo mostrado en la figura 2.
5. Un proceso para preparar el polimorfo de la reivindicación 1, que comprende agitar durante un tiempo que varía entre aproximadamente 2 a 48 horas una lechada de clorhidrato de irinotecan como Forma b o como amorfo, en acetonitrilo o en acetona.
6. Una composición farmacéutica que comprende una cantidad terapéuticamente efectiva del polimorfo de la reivindicación 1 como un ingrediente activo y un excipiente farmacéuticamente aceptable.

7. La composición de la reivindicación 6, en donde la composición es adecuada para administración inyectable.
8. La composición de la reivindicación 6, en donde la composición es adecuada para administración oral.
9. La composición de la reivindicación 6, en donde la composición está en una forma de dosis acuosa.
10. Un método para la preparación de una composición farmacéutica de clorhidrato de irinotecan que comprende mezclar una cantidad terapéuticamente efectiva del polimorfo de la reivindicación 1 con un excipiente farmacéuticamente aceptable.
11. Un método para tratar un paciente que tiene cáncer, que comprende administrar una cantidad terapéuticamente efectiva de un polimorfo de la reivindicación 1.
12. El método de la reivindicación 11, en donde el cáncer es un cáncer gastrointestinal.

13. El método de la reivindicación 12, en donde el cáncer gastrointestinal es un cáncer colorectal.
14. Un método para tratar un paciente que tiene cáncer, que comprende administrar la composición farmacéutica de la reivindicación 6.
15. El método de la reivindicación 14, en donde el cáncer es un cáncer gastrointestinal.
16. El método de la reivindicación 15, en donde el cáncer gastrointestinal es un cáncer colorectal.
17. Un método para la preparación de una solución acuosa de clorhidrato de irinotecan, que comprende disolver el polimorfo de la reivindicación 1 en una solución acuosa a temperatura ambiente.
18. El método de la reivindicación 17, en donde la solución acuosa tiene un valor de pH que varía entre aproximadamente 3,0 a aproximadamente 3,8.

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19. El método de la reivindicación 18, en donde la concentración final de clorhidrato de irinotecan es mayor que 10 mg/mL.

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FIGURA 1

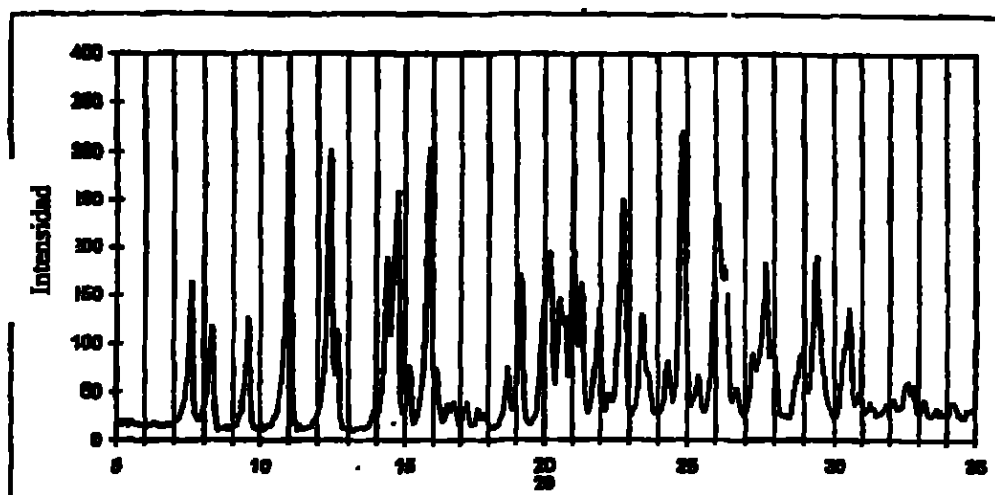
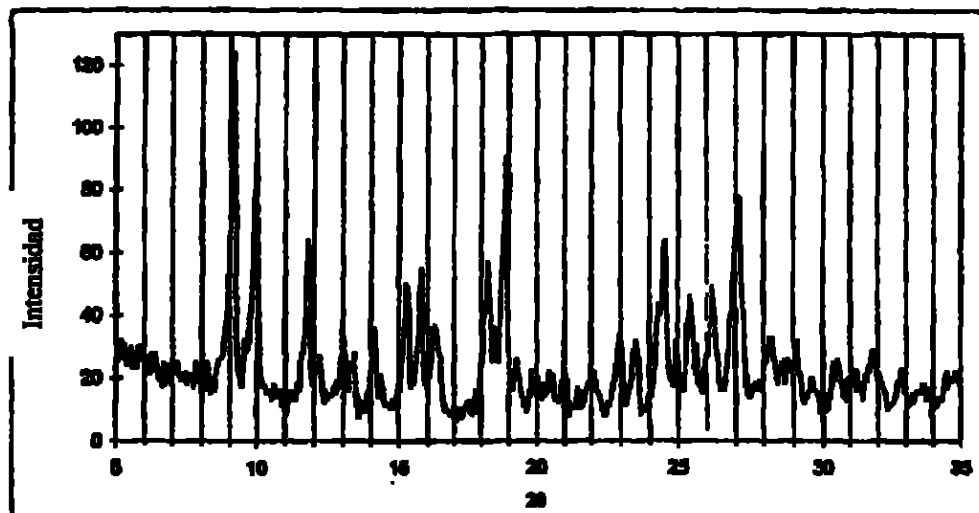


FIGURA 2



PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

PHARMACIA ITALIA SPA
Patent Department
Viale Pasteur, 10
I-20014 Milan
ITALIENOTIFICATION OF TRANSMITTAL OF
INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing
(day/month/year)

14/01/2004

Applicant's or agent's file reference
00760

IMPORTANT NOTIFICATION

International application No.

PCT/EP03/01948

International filing date (day/month/year)

26/02/2003

Priority date (day/month/year)

01/03/2002

Applicant

PHARMACIA ITALIA S.P.A.

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

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

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

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

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

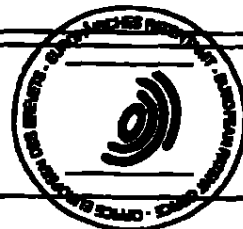
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Fax: (+31-70) 340-3016

Authorized officer

ROSSI C

Tel. (+49-89) 2399 2828



Form PCT/IPEA/116 (August 2002) P20473

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

(Rationalised Report according to the Notice of the President of the EPO published in the OJ11/2001)

Applicant's or agent's file reference 00760	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IP/EA/116)	
International application No. PCT/EP03/01948	International filing date (day/month/year) 26/02/2003	Priority date (day/month/year) 01/03/2002
International Patent Classification (IPC) or national classification and IPC C07D491/22		
Applicant PHARMACIA ITALIA S.P.A.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 2 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

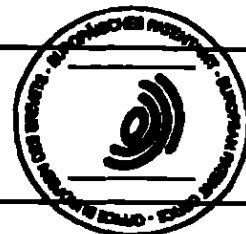
These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 15/09/2003	Date of completion of this report 09/01/2004
Name and mailing address of the IPEA/  European Patent Office, P.B. 3518 Patentlaan 1 NL-2280 HV Rijswijk - Netherlands Tel.: (+31-70) 340-2040 Fax: (+31-70) 340-3016	Authorized officer VERHULST W Tel. (+49-89) 2399 2828

Form PCT/IP/EA/09 (cover sheet) P20476 (October 2002)



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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No.

PCT/EP03/01948

I. Basis of the report

The basis of this international preliminary examination is the application as originally filed.

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

The question of whether the claimed invention appears to be novel, to involve an inventive step, or to be industrially applicable has not been the subject of the international preliminary examination in respect of the claims which have not been searched (Article 17(2)(a) or (3) and Rule 66.1(e) PCT); see also international search report).

V. Reasoned statement under Rule 66.2(a)(II) with regard to novelty, inventive step or industrial applicability

To the extent that the international preliminary examination has been carried out (see item III above), the following is pointed out:

In light of the documents cited in the international search report, it is considered that the invention as defined in at least some of the claims, which have been the subject of an international search report, does not appear to meet the criteria mentioned in Article 33(1) PCT, i.e. does not appear to be novel and/or to involve an inventive step (see international search report, in particular the documents cited X and/or Y and corresponding claim references).

PCT/EP03/01948

PATENT COOPERATION TREATY

BREVET
NOV 2003

PCT

INFORMATION CONCERNING ELECTED
OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 81.3)

From the INTERNATIONAL BUREAU

To:

PHARMACIA ITALIA S.P.A.
Patent Department
Viale Pasteur 10
I-20014 Nerviano (Milano)
Italy

Date of mailing (day/month/year)

28 October 2003 (28.10.03)

Applicant's or agent's file reference

00780

IMPORTANT INFORMATION

International application No.

PCT/EP03/01948

International filing date (day/month/year)

28 February 2003 (28.02.03)

Priority date (day/month/year)

01 March 2002 (01.03.02)

Applicant

PHARMACIA ITALIA S.P.A. et al

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

EP : AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI,
SK, TR

National : BG, CA, CN, DE, GB, IL, JP, KP, KR, MN, NO, PL, RO, RU, SK, US

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

AP : GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW

EA : AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

OA : BF, BJ, CF, CG, CI, CM, GA, GN, GO, GW, ML, MR, NE, SN, TD, TG

National : AE, AG, AL, AM, AT, AU, AZ, BA, BB, BR, BY, BZ, CH, CO, CR, CU, CZ, DK, DM, DZ, EC,
EE, ES, FI, GD, GE, GH, GM, HR, HU, ID, IN, IS, KE, KG, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,
MG, MK, MW, MX, MZ, NZ, OM, PH, PT, SC, SD, SE, SG, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC,
VN, YU, ZA, ZM, ZW

3. The applicant is reminded that he must enter the "national phase" before the expiration of 30 months from the priority date before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing, if prescribed, a translation of the international application (Article 38(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 38(3)(b) and Rule 74.1).

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

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

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 338.89.70

Authorized officer:

Patrick VILLECHAISE (Fax 338 8970)

Telephone No. (41-22) 338 8385

Form PCT/IB/332 (September 1997)

5834273

PATENT COOPERATION TREATY

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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To: PHARMACIA ITALIA SPA Patent Department Viale Pasteur, 10 I-20014 Milan ITALIE		Pharmacia & Upjohn S.p.A. BREVETT 28 OTT 2003 Mor	NOTIFICATION OF RECEIPT OF DEMAND BY COMPETENT INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY (PCT Rule 39.3(e) and 61.1(b), first sentence and Administrative Instructions, Section 601(a))
Applicant's or agent's file reference 00760		Date of mailing (day/month/year) 22-10-2003	
International application No. PCT/KP 03/ 01948		International filing date (day/month/year) 26/02/2003	Priority date (day/month/year) 01/03/2002
Applicant PHARMACIA ITALIA S.P.A.			

1. The applicant is hereby notified that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application:

15/09/2003

2. This date of receipt is:

- ☒ the actual date of receipt of the demand by this Authority (Rule 61.1(b)).
☐ the actual date of receipt of the demand on behalf of this Authority (Rule 39.3(e)).
☐ the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IP/EA/404), received the required corrections.

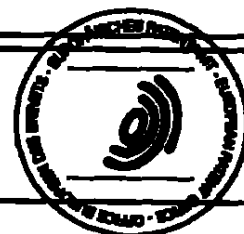
3. ☐ **ATTENTION:** That date of receipt is **AFTER** the expiration of 19 months from the priority date. Consequently, the election(s) made in the demand does (do) not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)). Therefore, the acts for entry into the national phase must be performed within 20 months from the priority date (or later in some Offices) (Article 22). For details, see the PCT Applicant's Guide, Volume II.

- ☐ (If applicable) This notification confirms the information given by telephone, facsimile transmission or in person.

4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

Name and mailing address of the IPEA/  European Patent Office, P.O. 5818 Patentstein 2 NL-2280 HV Rijswijk - Netherlands Tel.: (+31-70) 340-3040 Fax: (+31-70) 340-3016	Authorized officer ROSSI C Tel. (+31-70) 340-3322
--	--

Form PCT/IP/EA/402 (July 1998) P29452 (17/10/2003)



PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

PHARMACIA ITALIA SPA
Patent Department
Viale Pasteur, 10
I-20014 Milan
ITALIE

WRITTEN OPINION

(PCT Rule 66)

Date of mailing
(day/month/year)

22/10/2003

Applicant's or agent's file reference

00760

REPLY DUE

within 2 / 00 months/days
from the above date of mailing

International application No.

PCT/EP 03/ 01948

International filing date (day/month/year)

26/02/2003

Priority date (day/month/year)

01/03/2002

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

C07D491/22

Applicant

PHARMACIA ITALIA S.P.A.

1. This written opinion is the first drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I ☒ Basis of the opinionII ☐ PriorityIII ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicabilityIV ☐ Lack of unity of inventionV ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statementVI ☐ Certain documents citedVII ☐ Certain defects in the international applicationVIII ☐ Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4bis. For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 01/11/2004

Name and mailing address of the IPEA/

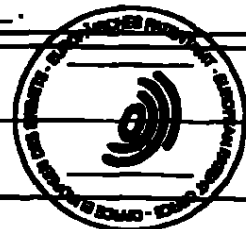


European Patent Office, P.O. Box 5018 Patentium 2
NL-2280 HV Rijswijk - Netherlands
Tel.: (+31-70) 340-2040
Fax: (+31-70) 340-3016

Authorized officer

Examiner

Formalities officer

(incl. extension of time limits)
Tel. (+49-89) 2399 2828

Form PCT/IPEA/408 (cover sheet) (march 2002)

WRITTEN OPINION

International application No PCT/EP 03/01948

I. Basis of the opinion

The basis of this written opinion is the application as originally filed.

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

The question of whether the claimed invention appears to be novel, to involve an inventive step, or to be industrially applicable has not been and will not be the subject of the international preliminary examination in respect of the claims which have not been searched (Article 17(2)(a) or (3) and Rule 66.1(a) PCT; see also international search report).

V. Reasoned statement under Rule 66.2(a)(II) with regard to novelty, inventive step or industrial applicability

1. To the extent that the international preliminary examination has been carried out (see item III above), the following is pointed out:
2. In light of the documents cited in the international search report, it is considered that the invention as defined in at least some of the claims, which have been the subject of an international search report, does not appear to meet the criteria mentioned in Article 33(1) PCT, i.e. does not appear to be novel and/or to involve an inventive step (see international search report, in particular the documents cited X and/or Y and corresponding claim references).
3. If amendments are filed, the applicant should comply with the requirements of Rule 66.8 PCT and indicate the basis of the amendments in the documents of the application as originally filed (Article 34 (2) (b) PCT) otherwise these amendments may not be taken into consideration for the establishment of the international preliminary examination report. The attention of the applicant is drawn to the fact that if the application contains an unnecessary plurality of independent claims, no examination of any of the claims will be carried out.

NB: Should the applicant decide to request detailed substantive examination, then an international preliminary examination report will normally be established directly. Exceptionally the examiner may draw up a second written opinion, should this be explicitly requested.

Pharmacia Italia S.p.A.
Centro Ricerca e Sviluppo
20014 Nerviano (MI) - Viale Pasteur, 18
Tel. 024838.1
www.pharmaciaitalia.it

PHARMACIA
Gruppo Pfizer Inc.

Messrs.
EUROPEAN PATENT OFFICE
P.B. 5818 Patentlaan 2
N.L. 2280 HV Riswijk
The Netherlands

Nerviano, September 11, 2003

Re: PCT Demand - CHAPTER II - Art. 31 PCT
International Patent Application No. PCT/EP03/01948, filed on 26/02/2003, priority date
claimed: 01/03/2002
Applicant: PHARMACIA ITALIA S.p.A.

Our ref: 00760

We request that the above identified International Application be the subject of International
Preliminary Examination according to the Patent Cooperation Treaty.
We are therefore enclosing herewith the following documents:

1. Demand form PCT/IPEA/401;
2. Fee calculation sheet incorporating a debit order;
3. Copy of the General Authorization.

Please acknowledge receipt of this matter by endorsing and returning the attached copy letter.

Yours faithfully

PHARMACIA ITALIA SpA

Alessandro Longoni
(Proxy, G.A. 44689)

Encl.

Sede Legale Via Robert Koch, 12 20132 Milano
Capitale Sociale € 25.000.000
Codice Fiscale e Partita IVA N. 03004600963
Registro Imprese N. 154376 Tribunale Milano
R.E.A. N. 1619301

80

Sheet No. 4.

International application No.
PCT/EP03/01948

Box No. VI CHECK LIST

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

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

For International Preliminary
Examining Authority use only

- | received | not received |
|--------------------------|--------------------------|
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |

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

- | | |
|---|---|
| 1. ☒ fee calculation sheet | 5. ☐ statement explaining lack of signature |
| 2. ☐ original separate power of attorney | 6. ☐ sequence listings in computer readable form |
| 3. ☐ original general power of attorney | 7. ☐ tables in computer readable form related to sequence listings |
| 4. ☒ copy of general power of attorney; reference number, if any: 44689 | 8. ☐ other (specify): |

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

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

Pharmacia Italia S.p.A.


Alessandra Longoni
(Proxy)

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

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

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.☐ The applicant has been informed accordingly.4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 90.5.5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCLUDED pursuant to Rule 82.

For International Bureau use only

Demand received from IPRA on:

21

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

IPEA/ EP

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:

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

For International Preliminary Examining Authority use only			
Identification of IPEA		Date of receipt of DEMAND	
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference 00780	
International application No. PCT/EP03/01948	International filing date (day/month/year) 28/02/2003	(Earliest) Priority date (day/month/year) 01/03/2002	
Title of invention CRYSTALLINE POLYMORPHIC FORM OF IRINOTECAN HYDROCHLORIDE			
Box No. II APPLICANT(S)			
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) Pharmacia Italia S.p.A. Via Robert Koch 1.2 20152 Milan ITALY		Telephone No. 0039 0248381	
		Facsimile No. 0039 0248382734	
		Teleprinter No.	
		Applicant's registration No. with the Office	
State (that is, country) of nationality: IT		State (that is, country) of residence: IT	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) FIORINO, Romualdo Via Del Caravaggio 14 20144 Milano ITALY			
State (that is, country) of nationality: IT		State (that is, country) of residence: IT	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) BARBUGIAN Natale Via Germana De Stael 1 20158 Milano ITALY			
State (that is, country) of nationality: IT		State (that is, country) of residence: IT	
☒ Further applicants are indicated on a continuation sheet.			

Sheet No. 2.

International application No.
PCT/EP03/01948

Continuation of Box No. II APPLICANT(S)

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

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

ZAMPIERI Massimo
Via L. Madorati 1
20052 Monza (Milano)
ITALYState (that is, country) of nationality:
ITState (that is, country) of residence:
IT

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

TOMASI Attilio
Via T. Guili 49
20147 Milano
ITALYState (that is, country) of nationality:
ITState (that is, country) of residence:
IT

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

State (that is, country) of nationality:

State (that is, country) of residence:

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

State (that is, country) of nationality:

State (that is, country) of residence:

☐ Further applicants are indicated on another continuation sheet.

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Sheet No. 3

International application No.
PCT/EP03/01948**Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE**The following person is ☐ agent ☐ common representativeand ☐ has been appointed earlier and represents the applicant(s) also for international preliminary examination.☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.Name and address: (Family name followed by given name; for a legal entity, full official designation.
The address must include postal code and name of country.)Pharmacia Italia S.p.A.
Patent Department
Viale Pasteur 10
20014 Nerviano (MI)
ITALY

Telephone No.

0039 0248383938

Facsimile No.

0039 0248385397

Teleprinter No.

Agent's registration No. with the Office

☒ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.**Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION****Statement concerning amendments***

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

☐ the international application as originally filed

the description

☐ as originally filed☐ as amended under Article 34

the claims

☐ as originally filed☐ as amended under Article 19 (together with any accompanying statement)☐ as amended under Article 34

the drawings

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

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

Language for the purposes of international preliminary examination: English☒ which is the language in which the international application was filed.☐ which is the language of a translation furnished for the purposes of international search.☐ which is the language of publication of the international application.☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.**Box No. V ELECTION OF STATES**

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

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

CHAPTER II

PCT

FEE CALCULATION SHEET

Annex to the Demand

International application No. PCT/EP03/01948	For International Preliminary Examining Authority use only	
Applicant's or agent's file reference 00760	Date stamp of the IPEA	
Applicant PCT/EP03/01948		
CALCULATION OF PRESCRIBED FEES		
1. Preliminary examination fee	EUR 1.530,00	P
2. Handling fee (Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.)	EUR 159,00	H
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box	EUR 1.689,00	
TOTAL		
MODE OF PAYMENT		
☒ authorization to charge deposit account with the IPEA (see below)	☐ cash	
☐ cheque	☐ revenue stamps	
☐ postal money order	☐ coupons	
☐ bank draft	☐ other (specify):	
AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT (This mode of payment may not be available at all IPEAs)		
☒ Authorization to charge the total fees indicated above.	IPEA/ <u>EP</u>	
☒ (This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.	Deposit Account No.: <u>28070039</u>	
	Date: <u>September 11, 2003</u>	
	Name: <u>Alessandra Longoni</u>	
	Signature: <u>[Signature]</u>	

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL SEARCHING AUTHORITY

To: PHARMACIA ITALIA SPA Patent Department Viale Pasteur, 10 I-20014 Nerviano (Milano) ITALY	Pharmacia BREVETTI 18 UG 2003 <i>ymol</i>	NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION (PCT Rule 44.1)
		Date of mailing (day/month/year) 18/07/2003
Applicant's or agent's file reference 00760	FOR FURTHER ACTION See paragraphs 1 and 4 below	
International application No. PCT/EP 03/01948	International filing date (day/month/year) 26/02/2003	
Applicant PHARMACIA ITALIA S.P.A.		

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
 34, chemin des Colombettes
 1211 Geneva 20, Switzerland
 Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Further action(s): The applicant is reminded of the following:

Shortly after 18 months from the priority date, the International application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the International application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for International publication.

Within 18 months from the priority date, a demand for International preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 18 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority  European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer John De Bruijn
--	---

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 28, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added" or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claims 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 48.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequences if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the international Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.3(a), first sentence).

Consequences with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/selected Office, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/selected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 00760	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, Item 5 below.	
International application No. PCT/EP 03/ 01948	International filing date (day/month/year) 26/02/2003	(Earliest) Priority Date (day/month/year) 01/03/2002
Applicant PHARMACIA ITALIA S.P.A.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

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

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. ☒ Certain claims were found unsearchable (see Box I).

3. ☐ Unity of invention is lacking (see Box II).

4. With regard to the title,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 35.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

INTERNATIONAL SEARCH REP RT

International Application No
PCT/EP 03/01948

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D491/22 A61K31/4375 A61P35/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

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

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

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SAWADA S ET AL: "SYNTHESIS AND ANTITUMOR ACTIVITY OF 20(S)-CAMPTOTHECIN DERIVATIVES: CARBAMATE-LINKED, WATER-SOLUBLE DERIVATIVES OF 7-ETHYL-10-HYDROXYCAMPTOTHECIN" CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN. TOKYO, JP, vol. 39, no. 6, 1 June 1991 (1991-06-01), pages 1446-1454, XP000653715 ISSN: 0009-2363 cited in the application Preparation of 6-27, mp=222-223°C, IR: 1747, 1715, 1655 ----- -/--	1-19

☒ Further documents are listed in the continuation of box C.☐ Patent family members are listed in annex.

* Special categories of cited documents:

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

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

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

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

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

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

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

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

Z document member of the same patent family

Date of the actual completion of the international search

10 July 2003

Date of mailing of the international search report

18/07/2003

Name and mailing address of the ISA

European Patent Office, P.O. 5518 Patentkan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 851 apo nl
Fax: (+31-70) 340-3016

Authorized officer

Diederens, J

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/01948

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HENEGAR K E ET AL: "PRACTICAL ASYMMETRIC SYNTHESIS OF (S)-4-ETHYL-7,8-DIHYDRO-4-HYDROXY-1 H-PYRANOL3,4-F INDOLIZINE-3,6,10(4H)-TRIONE, A KEY INTERMEDIATE FOR THE SYNTHESIS OF IRINOTECAN AND OTHER CAMPTOTHECIN ANALOGS" JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, US, vol. 62, no. 19, 1997, pages 6588-6597, XP002935575 ISSN: 0022-3263 cited in the application Preparation of Irinotecan: mp=259-260°C	1-19

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/01948

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

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

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 11-16 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

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

Remark on Protest

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

PATENT COOPERATION TREATY
BREVETTI16 APR 2003
her

From the RECEIVING OFFICE

PCT

To:

PHARMACIA ITALIA SPA
Patent Department
Viale Pasteur, 10
I-20014 Nerviano (Milano)
ITALIENOTIFICATION OF THE INTERNATIONAL
APPLICATION NUMBER AND OF THE
INTERNATIONAL FILING DATE

(PCT Rule 20.5(c))

Date of mailing
(day/month/year)

11 04 2003

Applicant's or agent's file reference
00760

IMPORTANT NOTIFICATION

International application No.

PCT/EP 03/ 01948

International filing date (day/month/year)

26/02/2003

Priority date (day/month/year)

01/03/2002

Applicant

PHARMACIA ITALIA S.P.A.

Title of the invention

1. The applicant is hereby notified that the international application has been accorded the international application number and the international filing date indicated above.
2. The applicant is further notified that the record copy of the international application was transmitted to the International Bureau on the above date of mailing.

3. ☐

Other: _____

* The International Bureau monitors the transmittal of the record copy by the receiving Office and will notify the applicant (with Form PCT/IB/301) of its receipt. Should the record copy not have been received by the expiration of 14 months from the priority date, the International Bureau will notify the applicant (Rule 22.1(c)).

Name and mailing address of the Receiving Office

European Patent Office, P.B. 2818 Patentium 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040
Fax: (+31-70) 340-3016

Authorized officer

Marc Sartor

FEL: 6602

Form PCT/RO/105 (Jul 1992)

1/5

PCT REQUEST

00760

Original (for SUBMISSION) - printed on 24.02.2003 10.45.30 AM

0	For receiving Office use only	
0-1	International Application No.	PCT/EP 03 / 01948
0-2	International Filing Date	26 FEB 2003 (27 02 2003)
0-3	Name of receiving Office and "PCT International Application"	EUROPEAN PATENT OFFICE PCT INTERNATIONAL APPLICATION
0-4	Form - PCT/RO/101 PCT Request	
0-4-1	Prepared using	PCT-EASY Version 2.92 (updated 01.01.2003)
0-6	Petition	
	The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-8	Receiving Office (specified by the applicant)	European Patent Office (EPO) (RO/EP)
0-7	Applicant's or agent's file reference	00760
I	Title of invention	CRYSTALLINE POLYMORPHIC FORM OF IRINOTECAN HYDROCHLORIDE
II	Applicant	
II-1	This person is:	applicant only
II-2	Applicant for	all designated States except US
II-4	Name	PHARMACIA ITALIA S.P.A.
II-5	Address:	Via Robert Koch, 1.2 I-20152 Milano Italy
II-6	State of nationality	IT
II-7	State of residence	IT
II-8	Telephone No.	+00390248381
II-9	Facsimile No.	+00390248382734
III-1	Applicant and/or inventor	
III-1-1	This person is:	applicant and inventor
III-1-2	Applicant for	US only
III-1-4	Name (LAST, First)	FORINO, Romualdo
III-1-5	Address:	Via del Caravaggio 14 I-20144 Milano Italy
III-1-6	State of nationality	IT
III-1-7	State of residence	IT

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00780

PCT REQUEST

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II-2	Applicant and/or inventor	
III-2-1	This person is:	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	BARBUGIAN, Natale
III-2-5	Address:	Via Germana De Stael 1 I-20158 Milano Italy
III-2-6	State of nationality	IT
III-2-7	State of residence	IT
II-3	Applicant and/or inventor	
III-3-1	This person is:	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	ZAMPIERI, Massimo
III-3-5	Address:	Via L. Modorati 1 I-20052 Monza (Milano) Italy
III-3-6	State of nationality	IT
III-3-7	State of residence	IT
II-4	Applicant and/or inventor	
III-4-1	This person is:	applicant and inventor
III-4-2	Applicant for	US only
III-4-4	Name (LAST, First)	TOMASI, Attilio
III-4-5	Address:	Via T. Gulli 49 I-20147 Milano Italy
III-4-6	State of nationality	IT
III-4-7	State of residence	IT
IV-1	Agent or common representative; or address for correspondence No agent or common representative has been appointed; the following special address should be used as:	address for correspondence
IV-1-1	Name	PHARMACIA ITALIA S.P.A.
IV-1-2	Address:	Patent Department Viale Pasteur 10 I-20014 Nerviano (Milano) Italy
IV-1-3	Telephone No.	+00390248383938
IV-1-4	Facsimile No.	+00390248385397

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PCT REQUEST

00780

Original (for SUBMISSION) - printed on 24.02.2003 10:45:30 AM

V	Designation of States	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT SE SI SK TR and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BY BE CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
V-3	Precautionary Designation Statement In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4B(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.	
V-4	Exclusion(s) from precautionary designations	NONE
VI-1	Priority claim of earlier national application	
VI-1-1	Filing date	01 March 2002 (01.03.2002)
VI-1-2	Number	60/360,684
VI-1-3	Country	US
VI-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)

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PCT REQUEST

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09760

VII	Declarations	Number of declarations	
VII-1	Declaration as to the identity of the inventor	-	
VII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	
IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	5	-
IX-2	Description	20	-
IX-3	Claims	3	-
IX-4	Abstract	1	EZABST00.TXT
IX-5	Drawings	1	-
IX-7	TOTAL	30	
	Accompanying items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-9	Original separate power of attorney	✓	-
IX-11	Copy of general power of attorney	reference no. 44689	-
IX-13	Priority document(s)	Item(s) VI-1	-
IX-17	PCT-EASY diskette	-	Diskette
IX-18	Figure of the drawings which should accompany the abstract		
IX-26	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative		
X-1-1	Name	PHARMACIA ITALIA S.P.A.	
X-1-2	Name of signatory	Alessandra Longoni	
X-1-3	Capacity	Proxy	

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	26 MAR 2003 (26.02.2003)
10-2	Drawings:	
10-2-1	Received	26 FEB 2003
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP

RO/E

PCT/EP 03/01948

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PCT REQUEST

Original (for SUBMISSION) - printed on 24.02.2003 10:45:30 AM

00700

10-8	Transmittal of search copy delayed until search fee is paid	
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FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	
------	--	--

SUPERINTENDENCIA Y EJERCICIO

Radicación: 8445877 65082363

Folios: 97

Fecha (AMB): 2004-09-01 17:31:42

Trazado : 011 PCT-PATENT 379 FASE INCI 411 PRESENTA

Destinatario: 2528 DIVISION DE NUEVAS INVENCIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
✓ PATENTE DE INVENCION	()	()
MODELO DE UTILIDAD	()	()
- Indicación de que se solicita la concesión de una patente.	()	()
- Datos de identificación del solicitante o de la persona que presenta la solicitud.	()	()
- Descripción de la invención.	()	()
- Dibujos de ser estos pertinentes.	()	()
- Comprobante de Pago de las tasas establecidas. (X)	()	()
COMPLETA (X)	INCOMPLETA ()	()
DISEÑO INDUSTRIAL ()		
- Indicación de que se solicita el registro de Diseño Industrial	()	()
- Datos de identificación del solicitante o de la persona que presenta la solicitud.	()	()
- Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	()	()
- Comprobante de pago de las tasas establecidas	()	()
COMPLETA ()	INCOMPLETA ()	()
ESQUEMA DE TRAZADO ()		
- Indicación de que solicita el registro de un Esquema de trazado.	()	()
- Datos de identificación del solicitante o de la persona que presenta La solicitud.	()	()
- Representación gráfica del esquema de trazado	()	()
- Comprobante de pago de las tasas establecidas.	()	()
COMPLETA ()	INCOMPLETA ()	()

Firma Responsable:

Claudia M Nueva

Fecha:

Bogotá, Septiembre 1 de 2004

2020
Bogotá D C

Doctor(a)
ALVARO CORREA ORDOÑEZ
 Apoderado
 PHARMACIA ITALIA S.P.A

Oficio N°
66636

ASUNTO:

Radicación N°	04-85877
Solicitud internacional	PCT/EP03/01948
Fecha inicio fase nacional	01/10/2004
Trámite	011
Evento	379
Actuación	430
Folios	002

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

- La solicitud no contiene la copia y traducción del documento en que consta la cesión del derecho de patente del inventor al solicitante o a su causante ó en su defecto la declaración bajo la regla PCT 4.17 junto con su traducción. (Art. 26-k) Decisión 486).
- La solicitud no contiene el poder debidamente otorgado, con el lleno de requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante, cuando éste fuere una persona jurídica.
- El solicitante debe presentar un nuevo título, que permita identificar la materia de la cual trata la solicitud, ya que el relacionado no se encuentra con la precisión necesaria para identificar claramente el objeto de la solicitud de patente (Regla 4.3 PCT, Art. 27, 27 Decisión 486, Circular Única 5.2.9).

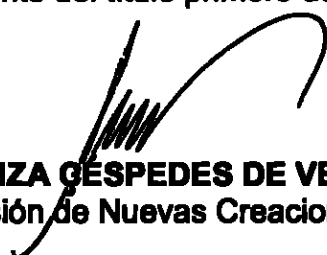
En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud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

Exp. - 0485877

100



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


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

El anterior requerimiento fue notificado por fijación en lista de fecha,
17 SET. 2004

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