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PATENTE DE INVENCIÓN

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54. **TÍTULO** PAMIDRONATO DISODICO INYECTABLE.

51. **CLASIFICACIÓN INTERNACIONAL** A 61 K 31/66.

71. **SOLICITANTE** Sicor Inc.

DOMICILIO Irvine, CA 92618, Estados Unidos de America.

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22. **BOGOTÁ, D. C.,** _____

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FORMULARIO ÚNICO DE SOLICITUD DE PATENTE

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ENTRADA EN FASE NACIONAL

1 SOLICITUD DE:

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.

☐ Capítulo I. ☒ Capítulo II.

2 SOLICITANTE (71)	Nombre: SICOR INC. Dirección: 19 Hughes, Irvine, CA 92618, Estados Unidos de América Nacionalidad o Domicilio: Estados Unidos Lugar de Constitución: Estados Unidos Teléfono: Fax: E-mail	**IDENTIFICACION** C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual____ Número _____
3 REPRESENTANTE O APODERADO	Nombre: RAMIRO CASTRO DUQUE Dirección: Cra. 7 No. 16-56 Piso 9 Teléfono: 380-2200 Fax: 380-2700 E-mail:	**IDENTIFICACION** C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual____ Número 170.322 TP 1003
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10 ANEXOS

- [x] Comprobante de pago de la tasa de presentación de la solicitud. $400.000
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [ ] Poderes, si fuere el caso.
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Copia del examen preliminar efectuado por la IPEA.
- [ ] Traducción del examen preliminar efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12x12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [x] Otros Tarjeta de propietarios.

11 FIGURA CARACTERÍSTICA:

12 Solicito la concesión de la patente

NOMBRE: RAMIRO CASTRO DUQUE

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(54) Title: INJECTABLE PAMIDRONATE DISODIUM

(57) Abstract: The invention includes a packaged liquid composition of a pamidronate alkaline salt in a sealed storage vessel having an inner surface which is non-reactive with the pamidronate alkaline salt composition.

INJECTABLE PAMIDRONATE DISODIUM

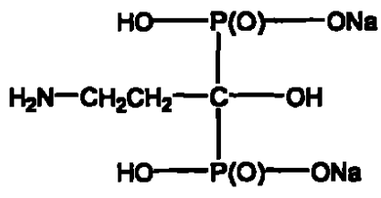
This application claims priority to U.S. Provisional Application Serial No. 60/288,293, filed May 2, 2001, the entire disclosure of which is hereby incorporated by reference.

FIELD OF THE INVENTION

This invention relates to storage stable injectable pamidronate alkaline salt solutions. The invention also relates to the preparation and use of these solutions in non-reactive containers.

BACKGROUND AND INTRODUCTION TO THE INVENTION

Pamidronate disodium, also known as disodium 3-amino-1-hydroxypropane-1,1-diphosphonate (I), is used in the treatment of diseases associated with calcium and/or



I

phosphate metabolism. Schmidt-Dünker, U.S. Patent No. 3,962,432, disclosed that aminoalkane-diphosphonic acids or their water-soluble salts are suitable for the therapeutic treatment of disorders associated with abnormal deposition of calcium salts, including inflammatory diseases, arteriosclerosis and osteoporosis.

Novartis Pharmaceutical Corp. currently markets Aredia®, a lyophilized pamidronate disodium pentahydrate, which is used to inhibit bone resorption and to treat hypercalcemia, as well as to treat metastatic bone pain. The Physicians Desk Reference 2000 reports that Aredia®, when reconstituted with Sterile Water for Injection, is capable of being stored under refrigeration for up to 24 hours. Stahl *et al.*, U.S. Patent

No. 4,711,880, disclosed a crystalline form of pamidronate disodium and a pharmaceutical preparation intended for enteral administration containing the crystalline salt.

SUMMARY OF THE INVENTION

This invention is directed towards a storage stable liquid pamidronate alkaline salt composition in a sealed storage vessel having an inner surface which is non-reactive with the pamidronate alkaline salt composition. The pamidronate alkaline salt may be, for example, pamidronate disodium or pamidronate dipotassium.

In one embodiment, the invention is directed to a packaged composition of a pamidronate alkaline salt in a sealed storage vessel. The pamidronate salt composition comprises a pamidronate alkaline salt, water, a sugar, a pharmaceutically acceptable base, and a pharmaceutically acceptable acid. The inner surface of the sealed storage vessel may be made of any material which is non-reactive with the pamidronate alkaline salt composition.

In another embodiment, the invention is directed to a method for preparing a packaged pamidronate alkaline salt composition by (a) combining a sugar with water; (b) combining the mixture of step (a) with pamidronic acid to form a pamidronic acid slurry; (c) adding to the pamidronic acid slurry sufficient aqueous solution of sodium hydroxide or potassium hydroxide to yield a solution having a pH of about 8.5; (d) adding to the resultant solution a pharmaceutically acceptable acid in an amount sufficient to lower the pH of the solution to about 6.5; (e) transferring the solution having a pH of about 6.5 into a vessel having an inner surface which does not react with the solution; and (f) sealing the vessel.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is based on the discovery that storage vessels made of glass may react with the pamidronate alkaline salt compositions. It is believed that glass may leach calcium or silicate which may react with pamidronate salt and thereby inhibit its therapeutic effectiveness. The present invention is directed to a storage stable liquid composition of a pamidronate alkaline salt in a sealed storage vessel having an inner

surface which is non-reactive with the pamidronate salt composition. Thus, the inner surface of the storage vessel is made of a material other than glass.

In one embodiment, the invention is directed to a packaged composition of a pamidronate alkaline salt in a sealed storage vessel. The pamidronate salt composition comprises a pamidronate alkaline salt, water, a sugar, a pharmaceutically acceptable base, and a pharmaceutically acceptable acid. The inner surface of the sealed storage vessel may be made of any material which is non-reactive with the pamidronate alkaline salt composition. The pamidronate alkaline salt may be, for example, pamidronate disodium or pamidronate dipotassium.

Typically, the sealed storage vessel is a vial. In one embodiment, the inner surface of the sealed storage vessel is made of plastic. For example, the inner surface of the sealed storage vessel may be made of polypropylene. Another type of non-glass vials, Resin CZ® vials, is available from West Pharmaceutical Services (Lionville, Pennsylvania).

Sugars, which may be used in the pamidronate alkaline salt compositions of the present invention, include mannitol, lactose and sucrose. Typically, the sugar is mannitol.

Pharmaceutically acceptable bases, which may be used in the pamidronate alkaline salt compositions of the present invention, include sodium hydroxide and potassium hydroxide.

Pharmaceutically acceptable acids, which may be used in the pamidronate alkaline salt compositions of the present invention, include phosphoric acid, nitric acid, sulfuric acid, hydrochloric acid, methanesulphonic acid, benzenesulphonoic acid, acetic acid, citric acid, lactic acid, propionic acid, tartaric acid, glutamic acid, maleic acid, ascorbic acid, fumaric acid, succinic acid, methyl sulfuric acid, and benzyl sulfonic acid. Typically, the pharmaceutically acceptable acid is phosphoric acid.

The compositions of the present invention typically have a pH between about 6.0 and about 9.0. Most often, the composition has a pH of about 6.5.

In another embodiment, the invention is directed to a method for preparing a packaged liquid pamidronate alkaline salt composition by (a) combining a sugar with

water; (b) combining the mixture of step (a) with pamidronic acid to form a pamidronic acid slurry; (c) adding to the pamidronic acid slurry sufficient aqueous solution of sodium hydroxide or potassium hydroxide to yield a solution having a pH of about 8.5; (d) adding to the resultant solution a pharmaceutically acceptable acid in an amount sufficient to lower the pH of the solution to about 6.5; (e) transferring the solution having a pH of about 6.5 into a vessel having an inner surface which does not react with the solution; and (f) sealing the vessel. Alternatively, a pamidronic acid aqueous slurry can be treated with aqueous sodium hydroxide or potassium hydroxide to form an aqueous solution of pamidronate disodium or pamidronate dipotassium. This solution can then be combined with mannitol and the resulting solution acidified to a pH of about 6.5 with, for example, phosphoric acid.

Sugars, which may be used in the method of this invention, include mannitol, lactose and sucrose. Typically, the sugar is mannitol.

Pharmaceutically acceptable acids, which may be used in the method of this invention, include phosphoric acid, nitric acid, sulfuric acid, hydrochloric acid, methanesulphonic acid, benzenesulphonoic acid, acetic acid, citric acid, lactic acid, propionic acid, tartaric acid, glutamic acid, maleic acid, ascorbic acid, fumaric acid, succinic acid, methyl sulfuric acid, and benzyl sulfonic acid. Typically, the pharmaceutically acceptable acid is phosphoric acid.

The inner surface of the storage vessel used in the method of the present invention may be made of any material which is non-reactive with the pamidronate alkaline salt composition of the invention. For example, the inner surface of the storage vessel may be made of plastic, such as polypropylene.

The pamidronate alkaline salt compositions of the present invention may be useful for treating diseases associated with calcium and/or phosphate metabolism in mammalian, and more preferably, in human patients. The particular carrier employed in these pharmaceutical compositions may vary depending upon the type of administration desired, *e.g.*, enteral, topical or parenteral.

In preparing the pharmaceutical compositions of the present invention in enteral liquid dosage forms (*e.g.*, solutions), typical pharmaceutical media such as water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like may be employed. For parenteral administration, a carrier will typically comprise sterile water although other ingredients, that aid in solubility or serve as preservatives, may also be included.

The pharmaceutical compositions of the present invention are generally administered in the form of a daily dosage unit at concentrations from about 1 μg/kg of body weight to about 500 mg/kg of body weight. Typically the compositions of the present invention are administered in a daily dosage of from about 10 μg/kg to about 250 mg/kg. Most often the compositions of the present invention are administered in a daily dosage of from about 20 μg/kg to about 100 mg/kg. As recognized by those skilled in the art, the particular quantity of pharmaceutical composition according to the present invention administered to a patient will depend upon a number of factors, including, without limitation, the biological activity desired, the condition of the patient, and tolerance for the drug.

Typically, pamidronate disodium is administered intravenously in dosages of 30 mg, 60 mg or 90 mg over an infusion period of either 4 or 24 hours.

Examples

The pamidronate disodium solution (3 mg/mL) was prepared by the following steps: Mannitol (470 mg) was added to Water for Injection with stirring. Solid pamidronic acid (25.3 mg) was added with stirring to form a slurry. 1N aqueous sodium hydroxide solution was added, with stirring, until a pH of at least 8.5 was reached and the solution was clear. 1M phosphoric acid was then added to adjust the pH to 6.5. Water for Injection was added to bring the volume total to 10 mL.

Formulation Example 1

An aqueous solution in sealed 10 mL plastic vials, containing a pamidronate disodium concentration of 3 mg/mL and having the following components:

Pamidronic Acid	2.53 mg/mL
Mannitol	47.0 mg/mL
Water for Injection	q.s. to 10 mL
Sodium Hydroxide	adjust pH to at least 8.5
Phosphoric Acid, NF	adjust pH to 6.5

Formulation Example 2

An aqueous solution in sealed 10 mL plastic vials, containing a pamidronate disodium concentration of 9 mg/mL and having the following components:

Pamidronic Acid	7.59 mg/mL
Mannitol	37.5 mg/mL
Water for Injection	q.s. to 10 mL
Sodium Hydroxide	adjust pH to at least 8.5
Phosphoric Acid, NF	adjust pH to 6.5

While 10 mL vials containing pamidronate disodium compositions containing pamidronate disodium at concentrations of 3 mg/mL and 9 mg/mL have been exemplified, solutions of different volumes and different concentrations of pamidronate disodium may be prepared according to the methods of the present invention.

Example 3

Pamidronate Disodium Injection

Lyophilized pamidronate disodium for injection, 30 mg/vial and 90 mg/vial, is commercially available in glass vials. Pamidronate disodium is a strong chelator and in solution it may extract calcium or silica from glass. Consequently, the reconstituted lyophilized product should be used within 24 hours after reconstitution. It is not expected that the extraction of silica or calcium from glass would be significant within such a short period of time.

Lyophilized pamidronate disodium for injection was reconstituted with water in two glass vials to provide two compositions having pamidronate disodium concentrations of 3 mg/mL and 9 mg/mL, respectively. The data shown in Table 1 demonstrate increasing levels of silicon in the solutions when the reconstituted product was kept in glass vials for an extended period of time. Higher levels of silicon are found in the 9 mg/mL solution than in the 3 mg/mL solution.

Table 1. Silicon Levels in Reconstituted Pamidronate Disodium for Injection Stored in Glass Vials at 27.5°C

Concentration of Pamidronate Disodium	Silicon/ µ/mL		
	2 months	5 months	8 months
3 mg/mL	6.4	8.6	11.0
9 mg/mL	12.4	18.3	21.6

Lyophilized pamidronate disodium for injection was reconstituted with water in two polypropylene vials to provide two compositions having pamidronate disodium concentrations of 3 mg/mL and 9 mg/mL, respectively. The data in Table 2 show that no measurable increase in silicon levels was detected over a period of 12 months for either the 3 mg/mL or the 9 mg/mL solution.

Table 2. Silicon Levels in Pamidronate Disodium Injection Stored in Polypropylene Vials at 27.5°C

Concentration of Pamidronate Disodium	Silicon/ µ/mL				
	Zero Time	3 months	6 Months	9 Months	12 Months
3 mg/mL	<1.8	<1.8	<1.8	<1.8	<1.8
9 mg/mL	<1.8	<1.8	<1.8	<1.8	<1.8

The silicon levels were monitored with the ICP method (Inductively Coupled Plasma). The method determines the silicon element that could originate either from silica, silicates, or silicone.

Typically, pharmaceutical manufacturers siliconize the rubber closures. Lubrication of rubber closures with polydimethylsiloxane fluids (PDMS), commonly called silicone oil, is critical to the processability and machinability of stoppers. The level

of siliconization is carefully controlled to prevent adsorption of silicone into elastomeric closures, which could leach into the reconstituted product. Such leaching could cause the solution to become hazy, indicating the presence of particulate matter.

Therefore, an additional experiment was performed to demonstrate that silicon levels found in the reconstituted pamidronate disodium for injection in glass vials were caused by the extraction of silica from the glass and not by the extraction of silicone adsorbed to the stoppers. The stoppers used for the lyophilized product typically have a larger product contact area than Teflon-faced stoppers used in the manufacture of pamidronate disodium injection in polypropylene vials.

The stoppers of the lyophilized pamidronate disodium for injection, 30 mg/vial and 90 mg/vial, were removed and the product was reconstituted with 10 mL of Sterile Water for Injection. Then the vials were stoppered using the same Teflon-faced stoppers as used for pamidronate disodium injection in polypropylene vials. Two weeks after the reconstitution the vials were analyzed for silicon content.

The results shown in Table 3 demonstrate that the silicon level in the reconstituted pamidronate disodium for injection, stoppered with the same stoppers as pamidronate disodium injection liquid formulation manufactured in polypropylene vials, exceeds, within 2 weeks, the silicon level found in the liquid product stored in plastic vials for 12 months.

Table 3. Silicon Levels in Reconstituted Pamidronate Disodium for Injection in Glass Vials Stoppered with Teflon-Faced Stoppers after Two Weeks at 27.5°C

Concentration of Pamidronate Disodium	Silicon/ μ/mL
	2 Weeks
3 mg/mL	2.6
9 mg/mL	4.9

These results support the beneficial use of sealed storage vessels having an inner surface which is non-reactive with pamidronate disodium or pamidronate dipotassium for injection.

While in accordance with the patent statutes, description of the preferred embodiments and processing conditions have been provided, the scope of the invention is not to be limited thereto or thereby. Various modifications and alterations of the present invention will be apparent to those skilled in the art without departing from the scope and spirit of the present invention.

Consequently, for an understanding of the scope of the present invention, reference is made to the following non-limiting enumerated embodiments.

What is claimed is:

1. A packaged composition comprising:

(a) an aqueous pamidronate disodium composition comprising:

(i) disodium pamidronate;

(ii) a sugar;

(iii) a pharmaceutically acceptable base; and

(iv) a pharmaceutically acceptable acid;

(v) water;

and

(b) a sealed storage vessel having an inner surface which is non-reactive with said pamidronate disodium composition.

2. A packaged composition according to claim 1, wherein said inner surface of said sealed storage vessel is comprised of plastic.

3. A packaged composition according to claim 2, wherein said inner surface of said sealed storage vessel is comprised of polypropylene.

4. A packaged composition according to claim 1, wherein said sugar is selected from the group of mannitol, lactose and sucrose.

5. A packaged composition according to claim 4, wherein said sugar is mannitol.

6. A packaged composition according to claim 5, wherein said pharmaceutically acceptable base is sodium hydroxide.

7. A packaged composition according to claim 6, wherein said pharmaceutically acceptable acid is selected from the group of phosphoric acid, sulfuric acid, hydrochloric acid, acetic acid, methyl sulfuric acid, and benzyl sulfonic acid.

8. A packaged composition according to claim 7, wherein said pharmaceutically acceptable acid is phosphoric acid.

9. A packaged composition according to claim 8, wherein said composition has a pH between about 6.0 and about 9.0.

10. A packaged composition according to claim 9, wherein said composition has a pH of about 6.5.

11. A packaged composition according to claim 1, wherein the concentration of pamidronate salt is from 3 mg/mL to 9 mg/mL.

12. A packaged composition according to claim 11, wherein the pamidronate salt is pamidronate disodium or pamidronate dipotassium.

13. A packaged composition according to claim 12, wherein the pamidronate salt is pamidronate disodium.

14. A method for preparing a packaged aqueous pamidronate disodium composition comprising:

(a) combining a sugar with water;

(b) combining the mixture of step (a) with pamidronic acid to form a pamidronic acid slurry;

(c) adding to said pamidronic acid slurry sufficient aqueous solution of sodium hydroxide to yield a solution having a pH of about 8.5;

(d) adding to the resultant solution a pharmaceutically acceptable acid in an amount sufficient to lower to pH of said solution to about 6.5;

(e) transferring said solution having a pH of about 6.5 into a vessel having an inner surface which does not react with said solution; and

(f) sealing said vessel.

15. A method according to claim 14, wherein said sugar is selected from the group of mannitol, lactose and sucrose.

16. A method according to claim 15, wherein said sugar is mannitol.

17.. A method according to claim 16, wherein said pharmaceutically acceptable acid is selected from the group of phosphoric acid, sulfuric acid, hydrochloric acid, acetic acid, methyl sulfuric acid, and benzyl sulfonic acid.

18. A method according to claim 17, wherein said acid is phosphoric acid.

19. A method according to claim 18, wherein said inner surface of said storage vessel is comprised of polypropylene.

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Para códigos de dos letras y otras abreviaturas, remítase a las "Notas Guía sobre Códigos y Abreviaturas" que aparece al comienzo de cada edición regular del Boletín Oficial PCT.

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(54) Título: PAMIDRONATO DISÓDICO INYECTABLE

(57) Extracto: La invención incluye una composición líquida envasada de una sal alcalina de pamidronato en un recipiente sellado para almacenamiento con una superficie interna que es no reactiva con la composición de sal alcalina de pamidronato.

PAMIDRONATO DISÓDICO INYECTABLE

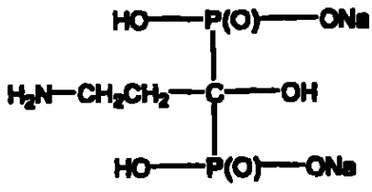
Esta solicitud reivindica prioridad para la Solicitud Provisional de los Estados Unidos Serie No. 60/288,293, presentada el 2 de mayo de 2001, cuya total divulgación se incorpora aquí por referencia.

CAMPO DE LA INVENCIÓN

Esta invención se relaciona con soluciones de sal alcalina de pamidronato inyectables, estables al almacenamiento. La invención se refiere igualmente a la preparación y uso de estas soluciones en envases no reactivos.

ANTECEDENTES E INTRODUCCIÓN A LA INVENCIÓN

Pamidronato disódico, también conocido como 3-amino-1-hidroxipropano-1,1-difosfonato (I) disódico, se usa en el tratamiento de enfermedades asociadas con metabolismo de calcio y/o



I

fosfato. Schmidt-Dünker, Patente de los Estados Unidos No. 3,962,432, divulgó que ácidos aminoalcano-difosfónicos o sus sales solubles en agua son aptos para el tratamiento terapéutico de trastornos asociados con deposición anormal de sales de calcio, incluyendo enfermedades inflamatorias, arteriosclerosis y osteoporosis.

Novartis Pharmaceutical Corp. comercializa actualmente Aredia®, un pentahidrato de pamidronato disódico liofilizado, que se emplea para inhibir la resorción ósea y para tratar la hipercalcemia, así como para tratar el dolor

metastático óseo. El Physicians Desk Reference 2000 informa que Aredia®, cuando se reconstituye con agua esterilizada para inyección, es susceptible de almacenarse bajo refrigeración durante un máximo de 24 horas. Stahl *y colaboradores*, Patente de los Estados Unidos No. 4,711,880, divulgó una forma cristalina de pamidronato disódico y una preparación farmacéutica prevista para administración enteral que contenía la sal cristalina.

SUMARIO DE LA INVENCIÓN

Esta invención se dirige a una composición de sal alcalina de pamidronato líquida, estable al almacenamiento, en un recipiente de almacenamiento sellado con una superficie interna que es no reactiva con la composición de sal alcalina de pamidronato. La sal alcalina de pamidronato puede ser, por ejemplo, pamidronato disódico o pamidronato dipotásico.

En una incorporación, la invención se dirige a una composición envasada de una sal alcalina de pamidronato en un recipiente de almacenamiento sellado. La composición de sal de pamidronato comprende una sal alcalina de pamidronato, agua, un azúcar, una base farmacéuticamente aceptable, y un ácido farmacéuticamente aceptable. La superficie interna del recipiente de almacenamiento sellado puede elaborarse de cualquier material que sea no reactivo con la composición de sal alcalina de pamidronato.

En otra incorporación, la invención se dirige a un método para preparar una composición envasada de sal alcalina de pamidronato (a) combinando un azúcar con agua; (b) combinando la mezcla de paso (a) con ácido pamidrónico para formar una lechada de ácido pamidrónico; (c) agregando a la lechada de ácido pamidrónico suficiente solución acuosa de hidróxido de sodio o hidróxido de potasio para producir una solución con un pH de alrededor de 8.5; (d) agregando a la solución resultante un ácido

farmacéuticamente aceptable en una cantidad suficiente para bajar el pH de la solución a alrededor de 6.5; (e) pasar la solución con un pH de alrededor de 6.5 a un recipiente con una superficie .nterna que no reacciona con la solución; y (f) sellando el recipiente.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

La presente invención se basa en el descubrimiento que recipientes de almacenamientos elaborados de vidrio pueden reaccionar con composición de sal alcalina de pamidronato. Se cree que el vidrio puede filtrar calcio o silicato el cual puede reaccionar con la sal de pamidronato e inhibir así su efectividad terapéutica. La presente invención se dirige a una composición líquida estable al almacenamiento de una sal alcalina de pamidronato en un recipiente de almacenamiento sellado con una superficie interna que es no reactiva con la composición de sal de pamidronato. Por consiguiente, la superficie interna del recipiente de almacenamiento se elabora de un material distinto al vidrio.

En una incorporación, la invención se dirige a una composición envasada de una sal alcalina de pamidronato en un recipiente de almacenamiento sellado. La composición de sal de pamidronato comprende una sal alcalina de pamidronato, agua, un azúcar, una base farmacéuticamente aceptable, y un ácido farmacéuticamente aceptable. La superficie interna del recipiente de almacenamiento sellado puede elaborarse de cualquier material que es no reactivo con la composición de sal alcalina de pamidronato. Por ejemplo, la sal alcalina de pamidronato puede ser pamidronato disódico o pamidronato dipotásico.

Típicamente, el recipiente de almacenamiento sellado es un frasco. En una incorporación, la superficie interna del recipiente de almacenamiento sellado se elabora de plástico. Por ejemplo, la superficie interna del recipiente de almacenamiento sellado puede elaborarse de

polipropileno. Otro tipo de frascos distintos de vidrio, frascos de resina CZ®, se obtiene de West Pharmaceutical Services (Lionville, Pennsylvania).

Azúcares, que pueden usarse en las composiciónes de sal alcalina de pamidronato de la presente invención, incluyen mannitol, lactosa y sucrosa. Típicamente, el azúcar es mannitol.

Bases farmacéuticamente aceptables, que pueden usarse en las composiciónes de sal alcalina de pamidronato de la presente invención, incluyen hidróxido de sodio e hidróxido de potasio.

Ácidos farmacéuticamente aceptables, que pueden usarse en las composiciónes de sal alcalina de pamidronato de la presente invención, incluyen ácido fosfórico, ácido nítrico, ácido sulfúrico, ácido clorhídrico, ácido metanosulfónico, ácido bencenosulfónico, ácido acético, ácido cítrico, ácido láctico, ácido propiónico, ácido tartárico, ácido glutámico, ácido maleico, ácido ascórbico, ácido fumárico, ácido succínico, ácido metilsulfúrico, y ácido bencilsulfónico. Típicamente, el ácido farmacéuticamente aceptable es ácido fosfórico.

Las composiciones de la presente invención típicamente tienen un pH entre alrededor de 6.0 y alrededor de 9.0. Muy a menudo, la composición tiene un pH de alrededor de 6.5.

En otra incorporación, la invención se dirige a un método para preparar una composición líquida envasada de sal alcalina de pamidronato (a) combinando un azúcar con agua; (b) combinando la mezcla de paso (a) con ácido pamidrónico para formar una lechada de ácido pamidrónico; (c) agregando a la lechada de ácido pamidrónico suficiente solución acuosa de hidróxido de sodio o hidróxido de potasio para producir una solución con un pH de alrededor de 8.5; (d) agregando a la solución resultante un ácido

farmacéuticamente aceptable en una cantidad suficiente para bajar el pH de la solución a alrededor de 6.5; (e) pasando la solución con un pH de alrededor de 6.5 a un recipiente con una superficie interna que no reacciona con la solución; y (f) sellando el recipiente. Alternativamente, una lechada acuosa de ácido pamidrónico puede tratarse con hidróxido de sodio acuoso o hidróxido de potasio para formar una solución acuosa de pamidronato disódico o pamidronato dipotásico. Esta solución puede combinarse entonces con mannitol y la solución resultante acidificarse a un pH de alrededor de 6.5 con ácido fosfórico, por ejemplo.

Azúcares, que pueden usarse en el método de esta invención, incluyen mannitol, lactosa y sucrosa. Típicamente, el azúcar es mannitol.

Ácidos farmacéuticamente aceptables, que pueden usarse en el método de esta invención, incluyen ácido fosfórico, ácido nítrico, ácido sulfúrico, ácido clorhídrico,. ácido metanosulfónico, ácido bencenosulfónico, ácido acético, ácido cítrico, ácido láctico, ácido propiónico, ácido tartárico, ácido glutámico, ácido maleico, ácido ascórbico, ácido fumárico, ácido succínico, ácido metilsulfúrico, y ácido bencilsulfónico. Típicamente, el ácido farmacéuticamente aceptable es ácido fosfórico.

La superficie interna del recipiente de almacenamiento usado en el método de la presente invención puede elaborarse de cualquier material que sea no reactivo con la composición de sal alcalina de pamidronato de la invención. Por ejemplo, la superficie interna del recipiente de almacenamiento puede elaborarse de plástico, tal como polipropileno.

Las composiciones de sal alcalina de pamidronato de la presente invención pueden ser útiles para tratar enfermedades asociadas con el metabolismo del calcio y/o fosfato en pacientes mamíferos, y más preferiblemente, en humanos. El portador particular empleado en estas

composiciones farmacéuticas puede variar dependiendo del tipo de administración deseado, *verbigracia*, enteral, tópica o parenteral.

En la preparación de composiciones farmacéuticas de la presente invención en formas de dosificación líquida enteral (*verbigracia*, soluciones), pueden emplearse medios farmacéuticos típicos tales como agua, glicoles, aceites, alcoholes, agentes saborizantes, preservantes, agentes colorántes y similares. Para administración parenteral, un portador comprenderá típicamente agua esterilizada, si bien pueden incluirse también otros ingredientes, que contribuyan a la solubilidad o sirvan como preservantes.

Las composiciones farmacéuticas de la presente invención se administran generalmente en la forma de una unidad de dosificación diaria en concentraciones de alrededor de 1 μg/kg de peso corporal a alrededor de 500 mg/kg de peso corporal. Típicamente las composiciones de la presente invención se administran en una dosificación diaria de alrededor de 10 μg/kg a alrededor de 250 mg/kg. Muy a menudo, las composiciones de la presente invención se administran en una dosificación diaria de alrededor de 20 μg/kg a alrededor de 100 mg/kg. Como se reconoce por las personas expertas en el arte, la cantidad particular de la composición farmacéutica de acuerdo con la presente invención administrada a un paciente dependerá de un número de factores, incluyendo, sin limitación, la actividad biológica deseada, la condición del paciente, y la tolerancia del fármaco.

Típicamente, el pamidronato disódico se administra intravenosamente en dosificaciones de 30 mg, 60 mg ó 90 mg durante un período de infusión de 4 ó 24 horas.

Ejemplos

La solución de pamidronato disódico (3 mg/mL) se preparó por los siguientes pasos: se agregó mannitol (470 mg) a agua para inyección con agitación. Se agregó ácido pamidrónico sólido (25.3 mg) con agitación para formar una lechada. Se agregó 1N de solución de hidróxido de sodio acuoso, con agitación, hasta que se alcanzó un pH de por lo menos 8.5 y la solución fue clara. Luego se agregó 1M de ácido fosfórico para ajustar el pH a 6.5. Se agregó agua para inyección para llevar el volumen total a 10 mL.

Formulación de Ejemplo 1

Una solución acuosa en frascos plásticos sellados de 10 mL, que contenía una concentración de pamidronato disódico de 3 mg/mL y que tenía los siguientes componentes:

Ácido pamidrónico	253 mg/mL
Mannitol	47.0 mg/mL
Agua para inyección	q.s. (en cantidad suficiente) a 10 mg/mL
Hidróxido de sodio	para ajustar pH a por lo menos 8.5
Ácido fosfórico, NF	para ajustar pH a 6.5

Formulación Ejemplo 2

Una solución acuosa en frascos sellados de plástico de 10 mL, que contenía una concentración de pamidronato disódico de 9 mg/mL y que tenía los siguientes componentes:

Ácido pamidrónico	7.59 mg/mL
Mannitol	37.5 mg/mL
Agua para inyección	q.s. (en cantida suficiente) a 10

	mg/mL
Hidróxido de sodio	para ajustar pH a por lo menos 8.5
Ácido fosfórico, NF	para ajustar pH a 6.5

Aunque se han ejemplificado frascos de 10 mL con composiciones de pamidronato disódico en concentraciones de 3 mg/mL y 9 mg/mL, pueden prepararse soluciones de diferentes volúmenes y diferentes concentraciones de pamidronato disódico de acuerdo con los métodos de la presente invención.

Ejemplo 3

Inyección de Pamidronato Disódico

Pamidronato disódico liofilizado para inyección, 30 mg/frasco y 90 mg/frasco, se obtiene comercialmente en frascos de vidrio. El pamidronato disódico es un fuerte agente quelante y, en solución, puede extraer calcio o sílice del vidrio. Por consiguiente, el producto liofilizado reconstituido debe usarse en un término de 24 horas después de la reconstitución. En un período de tiempo tan corto no se espera que la extracción de sílice o calcio del vidrio sea significativa.

Pamidronato disódico liofilizado para inyección se reconstituyó con agua en dos frascos de vidrio para proveer dos composiciones con concentraciones de pamidronato disódico de 3 mg/mL y 9 mg/mL, respectivamente. Los datos mostrados en Tabla 1 muestran niveles crecientes de silicio en las soluciones cuando el producto reconstituido se guardó en frascos de vidrio durante un período ampliado de tiempo. Niveles más altos de silicio se encuentran en la solución de 9 mg/mL que en la solución de 3 mg/mL.

Tabla 1. Niveles de Silicio en Pamidronato Disódico Reconstituido para Inyección Almacenado en Frascos de Vidrio a 27.5°C

Concentración de Pamidronato Disódico	Silicio/ µ/mL		
	2 meses	5 meses	8 meses
3 mg/mL	6.4	8.6	11.0
9 mg/mL	12.4	18.3	21.6

Pamidronato disódico liofilizado para inyección se reconstituyó con agua en dos frascos de polipropileno para proveer dos composiciones con concentraciones de pamidronato disódico de 3 mg/mL y 9 mg/mL, respectivamente. Los datos en Tabla 2 muestran que no se detectó un aumento cuantificable en los niveles de silicio durante un período de 12 meses para la solución de 3 mg/mL o la solución de 9 mg/mL.

Tabla 2. Niveles de Silicio en Inyección de Pamidronato Disódico Almacenado en Frascos de Polipropileno a 27.5°C

Concentración de Pamidronato Disódico	Silicio/ µ/mL				
	Tiempo Cero	3 meses	6 Meses	9 Meses	12 Meses
3 mg/mL	<1.8	<1.8	<1.8	<1.8	<1.8
9 mg/mL	<1.8	<1.8	<1.8	<1.8	<1.8

Los niveles de silicio se monitorearon con el método ICP (Plasma Acoplado Inductivamente). El método determina el elemento silicio que podría originarse de sílice, silicatos, o silicona.

Típicamente, los fabricantes de farmacéuticos recubren las tapas de caucho con silicona. La lubricación de los cierres de caucho con fluidos de polidimetilsiloxano (PDMS), denominado comúnmente aceite de silicona, es crítica para la procesabilidad y maquinabilidad de los tapones. El nivel de recubrimiento con silicona se controla cuidadosamente para prevenir la adsorción de silicona en los cierres elastoméricos, que podría filtrarse al producto reconstituido. Dicha filtración podría hacer que la solución se volviera brumosa, indicando la presencia de una sustancia particular.

En consecuencia, se realizó un experimento adicional para demostrar que los niveles de silicio en el pamidronato disódico reconstituido para inyección en frascos de vidrio fueron causados por la extracción de sílice del vidrio y no por la extracción de silicona adsorbida en los tapones. Los tapones utilizados para el producto liofilizado típicamente tienen un área de contacto mayor con el producto que los tapones usados con superficie de teflón empleados en la manufactura de la inyección de pamidronato disódico en frascos de polipropileno.

Se retiraron los tapones del pamidronato disódico liofilizado para inyección, 30 mg/frasco y 90 mg/frasco, y el producto se reconstituyó con 10 mL de agua esterilizada para inyección. Seguidamente los frascos se taparon empleando los mismos tapones con superficie de teflón que se utilizaron para la inyección de pamidronato disódico en frascos de polipropileno. Dos semanas después de la reconstitución los frascos se analizaron para detectar el contenido de silicio.

Los resultados mostrados en la Tabla 3 demuestran que el nivel de silicio en el pamidronato disódico reconstituido para inyección, tapado con los mismos tapones que la formulación líquida de inyección de pamidronato disódico manufacturada en frascos de polipropileno, supera, en el término de 2 semanas, el nivel de silicona encontrado en el producto líquido almacenado en frascos plásticos durante 12 meses.

Tabla 3. Niveles de Silicio en Pamidronato Disódico Reconstituido para Inyección en Frascos de Vidrio Tapados con Tapones con Superficie de Teflón después de Dos Semanas a 27.5°C

Concentración de Pamidronato Disódico	Silicio/ µ/mL
	2 semanas
3 mg/mL	2.6

9 mg/mL	4.9

Estos resultados apoyan el uso benéfico de recipientes sellados para almacenamiento con una superficie interna que es no reactiva con pamidronato disódico o pamidronato dipotásico para inyección.

Aunque, de acuerdo con los estatutos de patentes, se han expuesto la descripción de las incorporaciones preferidas y las condiciones de procesamiento, la órbita de la invención no se limita a, o por ellas. Diferentes modificaciones y alteraciones de la presente invención serán evidentes a las personas expertas en el arte sin desviarse de la órbita y el espíritu de la presente invención.

En consecuencia, para un entendimiento de la órbita de la presente invención, se hace referencia a las siguientes incorporaciones enumeradas y no limitantes.

Lo que se reivindica es:

1. Una composición envasada que comprende:

(a) una composición de pamidronato disódico acuoso que incluye:

(i) pamidronato disódico;

(ii) un azúcar;

(iii) una base farmacéuticamente aceptable; y

(iv) un ácido farmacéuticamente aceptable;

(v) agua;

y

(b) un recipiente de almacenamiento sellado que posee una superficie interna que no es reactiva con dicha composición de pamidronato disódico.

2. Una composición envasada de acuerdo con la Reivindicación 1, en donde dicha superficie interna de dicho recipiente de almacenamiento sellado está conformada por plástico.

3. Una composición envasada de acuerdo con la Reivindicación 2, en donde dicha superficie interna de dicho recipiente de almacenamiento sellado está conformada por polipropileno.

4. Una composición envasada de acuerdo con la Reivindicación 1, en donde dicho azúcar se selecciona del grupo de mannitol, lactosa y sucrosa.

5. Una composición envasada de acuerdo con la Reivindicación 4, en donde dicho azúcar es mannitol.

6. Una composición envasada de acuerdo con la Reivindicación 5, en donde dicha base farmacéuticamente aceptable es hidróxido de sodio.

7. Una composición envasada de acuerdo con la Reivindicación 6, en donde dicho ácido farmacéuticamente aceptable se selecciona del grupo de ácido fosfórico, ácido sulfúrico, ácido clorhídrico, ácido acético, ácido metilsulfúrico, y ácido bencilsulfónico.

8. Una composición envasada de acuerdo con la Reivindicación 7, en donde dicho ácido farmacéuticamente aceptable es ácido fosfórico.

9. Una composición envasada de acuerdo con la Reivindicación 8, en donde dicha composición tiene un pH entre alrededor de 6.0 y alrededor de 9.0.

10. Una composición envasada de acuerdo con la Reivindicación 9, en donde dicha composición tiene un pH de alrededor de 6.5.

11. Una composición envasada de acuerdo con la Reivindicación 1, en donde la concentración de sal de pamidronato es de 3 mg/mL a 9 mg/mL.

12. Una composición envasada de acuerdo con la Reivindicación 11, en donde la sal de pamidronato es pamidronato disódico o pamidronato dipotásico.

13. Una composición envasada de acuerdo con la Reivindicación 12, en donde la sal de pamidronato es pamidronato disódico.

14. Un método para preparar una composición envasada de pamidronato disódico acuoso que comprende:

(a) combinar un azúcar con agua;

(b) combinar la mezcla de paso (a) con ácido pamidrónico para formar una lechada de ácido pamidrónico;

(c) agregar a dicha lechada de ácido pamidrónico suficiente solución acuosa de hidróxido de sodio para producir una solución que tenga un pH de alrededor de 8.5;

(d) agregar a la solución resultante un ácido farmacéuticamente aceptable en una cantidad suficiente para bajar el pH de dicha solución a alrededor de 6.5;

(e) pasar dicha solución con un pH de alrededor de 6.5 a un recipiente que posee una superficie interna que no reacciona con dicha solución; y

(f) sellar dicho recipiente.

15. Un método de acuerdo con la Reivindicación 14, en donde dicho azúcar se selecciona del grupo de mannitol, lactosa y sucrosa.

16. Un método de acuerdo con la Reivindicación 15, en donde dicho azúcar es mannitol.

17. Un método de acuerdo con la Reivindicación 16, en donde dicho ácido farmacéuticamente aceptable se selecciona del grupo de ácido fosfórico, ácido sulfúrico, ácido clorhídrico, ácido acético, ácido metilsulfúrico, y ácido bencilsulfónico.

18. Un método de acuerdo con la Reivindicación 17, en donde dicho ácido es ácido fosfórico.

19. Un método de acuerdo con la Reivindicación 18, en donde dicha superficie interna de dicho recipiente de almacenamiento está conformada por polipropileno.

TRANSMITTAL LETTER TO THE UNITED STATES RECEIVING OFFICE

Date	May 1, 2002
International Application No.	
Attorney Docket No.	30589.014.WO

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I. Certification under 37 CFR 1.10 (if applicable)

EL675945592US	May 1, 2002
Express Mail mailing number	Date of Deposit

I hereby certify that the application/correspondence attached hereto is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to Assistant Commissioner for Patents, Washington, D.C. 20231.

Josh Gibbs	
Signature of person mailing correspondence	Typed or printed name of person mailing correspondence

II. ☑ **New International Application**

TITLE	INJECTABLE PAMIDRONATE DISODIUM	Earliest priority date (Day/Month/Year): 02/05/01

SCREENING DISCLOSURE INFORMATION: In order to assist in screening the accompanying international application for purposes of determining whether a license for foreign transmittal should and could be granted and for other purposes, the following information is supplied. (Note: check as many boxes as apply):

A. ☐ The invention disclosed was not made in the United States.

B. ☐ There is no prior U.S. application relating to this invention.

C. ☐ The following prior U.S. application(s) contain subject matter which is related to the invention disclosed in the attached international application. (*NOTE: priority to these applications may or may not be claimed on form PCT/RO/101 (Request) and this listing does not constitute a claim for priority.*)

application no.		filed on	
application no.		filed on	

D. ☑ The present international application contains additional subject matter not found in the prior U.S. application(s) identified in paragraph C. above. The additional subject matter is found on pages [ ] and ☑ **DOES NOT ALTER** ☐ **MIGHT BE CONSIDERED TO ALTER** the general nature of the invention in a manner which would require the U.S. application to have been made available for inspection by the appropriate defense agencies under 35 U.S.C. 181 and 37 CFR 5.1. See 37 CFR 5.15

III. ☐ **A Response to an Invitation from the RO/US. The following document(s) is(are) enclosed:**

A. ☐ A Request for An Extension of Time to File a Response

B. ☐ A Power of Attorney (General or Regular)

C. ☐ Replacement pages:

pages		of the request (PCT/RO/101)	pages		of the figures
pages		of the description	pages		of the abstract
pages		of the claims			

D. ☐ Submission of Priority Documents

Priority document		Priority document	

E. ☐ Fees as specified on attached Fee Calculation sheet form PCT/RO/101 annex

IV. ☐ **A Request for Rectification under PCT 91** ☐ **A Petition** ☐ **A Sequence Listing Diskette**

V. ☐ **Other (please specify):**

The person signing this form is the:

☐ Applicant	Richard H. Pagliery
☑ Attorney/Agent (Reg. No.) 44,276	Typed name of signer
☐ Common Representative	Richard Paglieri
	Signature

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TRANSMITTAL LETTER TO THE UNITED STATES RECEIVING OFFICE

Date	October 29, 2002
International Application No.	PCT/US02/13801
Attorney Docket No.	30569.014.WO

I. Certification under 37 CFR 1.10 (If applicable)

EL675947457US	October 29, 2002
Express Mail mailing number	Date of Deposit

I hereby certify that the application/correspondence attached hereto is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to Assistant Commissioner for Patents, Washington, D.C. 20231.

Megan Massey	Megan A. Massey
Signature of person mailing correspondence	Typed or printed name of person mailing correspondence

II. ☐ New International Application

TITLE		Earliest priority date (Day/Month/Year)

SCREENING DISCLOSURE INFORMATION: In order to assist in screening the accompanying international application for purposes of determining whether a license for foreign transmittal should and could be granted and for other purposes, the following information is supplied. (Note: check as many boxes as apply):

A. ☐ The invention disclosed was not made in the United States.

B. ☐ There is no prior U.S. application relating to this invention.

C. ☐ The following prior U.S. application(s) contain subject matter which is related to the invention disclosed in the attached international application. *(NOTE: priority to these applications may or may not be claimed on form PCT/RO/101 (Request) and this listing does not constitute a claim for priority.)*

application no.		filed on	
application no.		filed on	

D. ☐ The present international application contains additional subject matter not found in the prior U.S. application(s) identified in paragraph C. above. The additional subject matter is found on pages

and ☐ **DOES NOT ALTER** ☐ **MIGHT BE CONSIDERED TO ALTER** the general nature of the invention in a manner which would require the U.S. application to have been made available for inspection by the appropriate defense agencies under 35 U.S.C. 181 and 37 CFR 5.1. See 37 CFR 5.15

III. ☐ A Response to an Invitation from the RO/US. The following document(s) is(are) enclosed:

A. ☐ A Request for An Extension of Time to File a Response

B. ☐ A Power of Attorney (General or Regular)

C. ☐ Replacement pages:

pages		of the request (PCT/RO/101)	pages		of the figures
pages		of the description	pages		of the abstract
pages		of the claims			

D. ☐ Submission of Priority Documents

Priority document		Priority document	

E. ☐ Fees as specified on attached Fee Calculation sheet form PCT/RO/101 annex

IV. ☐ A Request for Rectification under PCT 91 ☐ A Petition ☐ A Sequence Listing Diskette

V. ☑ Other (please specify):

Transmittal letter (1 pg.); PCT-Demand Chapter II (3 pgs.); PCT Fee Calculation Sheet (1 pg.); Check for $636.00 and Return postcard.

The person signing this form is the:

☐ Applicant	Richard H. Pagliery
☑ Attorney/Agent (Reg. No.) 44,276	Typed name of signer
☐ Common Representative	Richard Pagliery
	Signature

28

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/ US

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
		30569.014.WO
International application No.	International filing date *(day/month/year)*	(Earliest) Priority date *(day/month/year)*
PCT/US02/13801	01 May 2002	02 May 2001
Title of invention		
INJECTABLE PAMIDRONATE DISODIUM		

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.)*	Telephone No.
SICOR Inc. 19 Hughes Irvine, CA 92618 United States of America	(949) 455-4700
	Facsimile No. (949) 855-8210
	Teleprinter No.
	Applicant's registration No. with the Office

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

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.)*

MIREJOVSKY, Doria
19151 Sierra Maria
Irvine, CA 92612
United States of America

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
NL	US

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.)*

BRITTAIN, Jason Edward
31882 Old Hickory Road
Trabuco Canyon, CA 92679
United States of America

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

☐ Further applicants are indicated on a continuation sheet.

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Sheet No. 2

International application No.
PCT/US02/13801

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

The following person is ☒ agent ☐ common representative

and ☒ 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.)*

PAGLIERY, Richard H.
BROBECK, PHLEGER & HARRISON LLP
12390 El Camino Real
San Diego, CA 92130
United States of America

Telephone No.
(858) 720-2500

Facsimile No.
(858) 720-2555

Teleprinter No.

Agent's registration No. with the Office
44,276

☐ 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 34

2. ☐ 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:

International application No. PCT/US02/13801 30

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:			For International Preliminary Examining Authority use only: received	not received
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	☐	☐

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

1. ☒ fee calculation sheet
2. ☐ original separate power of attorney
3. ☐ original general power of attorney
4. ☐ copy of general power of attorney; reference number, if any:
5. ☐ statement explaining lack of signature
6. ☐ sequence listing in computer readable form
7. ☒ other *(specify)*: Transmittal letter; Check in the amount of $636.00; and Return Postcard

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).

Richard H. Pagliery

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:
2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):
3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. ☐ The applicant has been informed accordingly.
4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.
5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

CHAPTER II

PCT

FEE CALCULATION SHEET

Annex to the Demand

International application No. PCT/US02/13801	For International Preliminary Examining Authority use only
Applicant's or agent's file reference 30569.014.WO	Date stamp of the IPEA

Applicant

SICOR Inc.

CALCULATION OF PRESCRIBED FEES

1. Preliminary examination fee	$490.00 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.)*	$146.00 H	
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box	$636.00 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)

IPEA/ US

☐ Authorization to charge the total fees indicated above.

☒ *(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.: 50-1273

Date: October 29, 2002

Name: Richard H. Pagliery

Signature: Richard Pagliery

BROBECK PHLEGER & HARRISON LLP ATTORNEYS AT LAW

BROBECK, PHLEGER & HARRISON LLP
ATTORNEYS AT LAW
12390 EL CAMINO REAL
SAN DIEGO, CA 92130

Wachovia Bank, N.A.
Greenville, South Carolina
In cooperation with & Payable if Desired at
Wells Fargo Bank, N.A.
4789-501677

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832

NO. 5500461

CHECK NO.

DATE
10-29-02

PAY Six Hundred Thirty Six and NO/100 Dollars

$636.00

TO THE ORDER OF COMMISSIONER OF PATENTS and TRADEMARKS

BROBECK, PHLEGER & HARRISON LLP

BY _____

AMOUNT NOT TO EXCEED $5,000.00

THE BACK OF THIS DOCUMENT CONTAINS AN ARTIFICIAL WATERMARK THAT READS "BROBECK, PHLEGER & HARRISON." HOLD AT AN ANGLE TO VIEW.

⑈5500461⑈ ⑆053200019⑆ 5404791 77⑈

BROBECK, PHLEGER & HARRISON LLP 12390 EL CAMINO REAL • SAN DIEGO, CA 92130

NO. 5500461

PAYEE:

CHECK NO:

VENDOR ID:

CHECK DATE:

INVOICE NUMBER	INVOICE DATE	DESCRIPTION	AMOUNT
	10-29-02	Filing Chapter II Demand. #030569.0014	$636.00

CHAPTER II DEMAND

Please acknowledge receipt of the following by affixing hereon the Patent and Trademark Office date stamp and returning this card to our office.

Applicant(s): SICOR Inc. **Client:** SICOR Inc.
Serial No.: PCT/US02/13801 **Filed:** May 1, 2002
Attorney: Richard H. Pagliery

INJECTABLE PAMIDRONATE DISODIUM

Docket No.: 30569.014.WO
Date of Deposit: October 29, 2002
Express Mail: EL675947457US
Enclosure(s): Transmittal Letter (1 pg.); PCT-Chapter II Demand (3 pgs.); PCT Fee Calculation Sheet (1 pg.); Check in the amount of $636.00.

33

EL675947457US

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EXPRESS MAIL
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ance Clerk Initials	Total Postage & Fees $	Employee Signature	
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		Signature of Addressee or Agent X	
		Name - Please Print X	

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Label 11-F July 1997

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☐ WAIVER OF SIGNATURE (Domestic Only): Additional merchandise insurance is void if waiver of signature is requested. I wish delivery to be made without obtaining signature of addressee or addressee's agent (if delivery employee judges that articles can be left in secure location) and authorize delivery employee to sign Proof of Delivery on my behalf. ☐ NO DELIVERY

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PHONE 858 720 2500

GER & HARRISON
INO REAL
CA 92130-2081

D H. PAGLIERO
2014.WD. LHP

TO: (PLEASE PRINT) PHONE ( )

COMMISSIONER FOR PATENTS
~~BOX PATENT APPLICATION~~ PCT
WASHINGTON DC 20231-0001

BOX PCT

R PICKUP OR TRACKING CALL 1-800-222-1811 www.usps.gov

92.340

RECEIVED
JUL 16 2003
Paul Hastings

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
RICHARD H. PAGLIERY
BROBECK, PHLEGER & HARRISON LLP
12390 El CAMINO REAL
SAN DIEGO, CA 92130

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing (day/month/year)	11 JUL 2003

Applicant's or agent's file reference	IMPORTANT NOTIFICATION
30569.014.WO	

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/US02/13801	01 May 2002 (01.05.2002)	02 May 2001 (02.05.2001)

Applicant

SICOR INC.

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.

Name and mailing address of the IPEA/US	Authorized officer
Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450	Sybille Delacroux-Muirheid Telephone No. 703-308-1235
Facsimile No. (703)305-3230	

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 30569.014.WO	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US02/13801	International filing date *(day/month/year)* 01 May 2002 (01.05.2002)	Priority date *(day/month/year)* 02 May 2001 (02.05.2001)
International Patent Classification (IPC) or national classification and IPC IPC(7): A61K 31/66 and US Cl.: 514/107; 562/13		
Applicant SICOR INC.		

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 3 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 Ø sheets.

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

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of report 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	Date of completion of this report
29 October 2002 (29.10.2002)	27 June 2003 (27.06.2003)
Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703)305-3230	Authorized officer Sylvia D. Roberts for Cybille Delacroix-Muirheid Telephone No. 703-308-1235

Form PCT/IPEA/409 (cover sheet)(July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US02/13801

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I. Basis of the report

1. With regard to the elements of the international application:*

☒ the international application as originally filed.

☒ the description:
pages 1-9 as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the claims:
pages 10-12, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the drawings:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☐ the sequence listing part of the description:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

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

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

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

☐ contained in the international application in printed form.

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

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to *this* Authority in computer readable form.

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

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

4. ☒ The amendments have resulted in the cancellation of:

☒ the description, pages NONE

☒ the claims, Nos. NONE

☒ the drawings, sheets/fig NONE

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

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

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

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US02/13801

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V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims	1-19	YES
	Claims	NONE	NO
Inventive Step (IS)	Claims	1-19	YES
	Claims	NONE	NO
Industrial Applicability (IA)	Claims	1-19	YES
	Claims	NONE	NO

2. CITATIONS AND EXPLANATIONS

Upon further consideration of the cited reference, it is the Examiner's position that claims 1-19 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the claimed packaged aqueous pamidronate disodium solution in a non-reactive sealed storage vessel nor does it disclose the claimed method of making an aqueous palmidronate solution and sealing it in a non-reactive vessel. The prior art to SHINAL (6,160,165 A) appears to disclose a method of making and packaging an anhydrous palmidronate composition.

Claims 1-19 meet the criteria set out in PCT Article 33(4), because the claimed inventions can be made or used in industry.

PATENT COOPERATION TREATY

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From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF RECEIPT OF RECORD COPY

(PCT Rule 24.2(a))

To:

PAGLIERY, Richard, H.
Brobeck, Phleger & Harrison, LLP
12390 El Camino Real
San Diego, CA 92130
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year)	IMPORTANT NOTIFICATION
08 July 2002 (08.07.02)	
Applicant's or agent's file reference	**International application No.**
30569.014.WO	PCT/US02/13801

The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

SICOR INC. (for all designated States except US)
MIREJOVSKY, Dorla et al (for US)

International filing date	:	01 May 2002 (01.05.02)
Priority date(s) claimed	:	02 May 2001 (02.05.01)
Date of receipt of the record copy by the International Bureau	:	04 June 2002 (04.06.02)
List of designated Offices	:	

AP :GH,GM,KE,LS,MW,MZ,SD,SL,SZ,TZ,UG,ZM,ZW
EA :AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
EP :AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE,TR
OA :BF,BJ,CF,CG,CI,CM,GA,GN,GQ,GW,ML,MR,NE,SN,TD,TG
National :AE,AG,AL,AM,AT,AU,AZ,BA,BB,BG,BR,BY,BZ,CA,CH,CN,CO,CR,CU,CZ,DE,DK,DM,DZ,
EC,EE,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KP,KR,KZ,LC,LK,LR,LS,LT,LU,
LV,MA,MD,MG,MK,MN,MW,MX,MZ,NO,NZ,OM,PH,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TN,TR,
TT,TZ,UA,UG,US,UZ,VN,YU,ZA,ZM,ZW

ATTENTION

The applicant should carefully check the data appearing in this Notification. In case of any discrepancy between these data and the indications in the international application, the applicant should immediately inform the International Bureau.

In addition, the applicant's attention is drawn to the information contained in the Annex, relating to:

- [X] time limits for entry into the national phase - see updated important information (as of April 2002)
- [ ] confirmation of precautionary designations (if applicable)
- [ ] requirements regarding priority documents (if applicable)

A copy of this Notification is being sent to the receiving Office and to the International Searching Authority.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer: Jocelyn JEANNEROT
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.38

PCT

REQUEST

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

For receiving Office use only

International Application No. 39

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* 30569.014.WO

Box No. I TITLE OF INVENTION

INJECTABLE PAMIDRONATE DISODIUM

Box No. II APPLICANT ☐ This person is also inventor

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

SICOR Inc.
19 Hughes
Irvine, CA 92618
United States of America

Telephone No. (949) 455-4700

Facsimile No. (949) 855-8210

Teleprinter No.

Applicant's registration No. with the Office

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

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

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

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

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

MIREJOVSKY, Dorla
19151 Sierra Maria
Irvine, CA 92612
United States of America

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

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

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

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

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

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

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

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

PAGLIERY, Richard H.
Brobeck, Phleger & Harrison LLP
12390 El Camino Real
San Diego, CA 92130
United States of America

Telephone No. (858) 720-2500

Facsimile No. (858) 720-2555

Teleprinter No.

Agent's registration No. with the Office 44,276

☐ **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.

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

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

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*	This person is:
BRITTAIN, Jason Edward 31882 Old Hickory Road Trabuco Canyon, CA 92679 United States of America	☐ applicant only ☒ applicant and inventor ☐ inventor only *(If this check-box is marked, do not fill in below.)* Applicant's registration No. with the Office
State *(that is, country)* of nationality: US	State *(that is, country)* of residence: US

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

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*	This person is:
	☐ applicant only ☐ applicant and inventor ☐ inventor only *(If this check-box is marked, do not fill in below.)* Applicant's registration No. with the Office
State *(that is, country)* of nationality:	State *(that is, country)* of residence:

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

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*	This person is:
	☐ applicant only ☐ applicant and inventor ☐ inventor only *(If this check-box is marked, do not fill in below.)* Applicant's registration No. with the Office
State *(that is, country)* of nationality:	State *(that is, country)* of residence:

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

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*	This person is:
	☐ applicant only ☐ applicant and inventor ☐ inventor only *(If this check-box is marked, do not fill in below.)* Applicant's registration No. with the Office
State *(that is, country)* of nationality:	State *(that is, country)* of residence:

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

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

Box No. V DESIGNATION OF STATES *Mark the applicable check-boxes below; at least one must be marked.*

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

Regional Patent

☒ **AP** **ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZM Zambia, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

☒ **EA** **Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT

☒ **EP** **European Patent:** AT Austria, BE Belgium, CH & LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT

☒ **OA** **OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GQ Equatorial Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

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

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

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

☐	☐	☐
☐	☐	☐

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

Supplemental Box *If the Supplemental Box is not used, this sheet should not be included in the request.*

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1. If, in any of the Boxes, except Boxes Nos. VIII(i) to (v) for which a special continuation box is provided, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No...." (indicate the number of the Box) and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:

(i) If more than two persons are to be indicated as applicants and/or inventors and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;

(ii) if, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;

(iii) if, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;

(iv) if, in addition to the agent(s) indicated in Box No. IV, there are further agents: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;

(v) if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "continuation" or "continuation-in-part": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;

(vi) if, in Box No. VI, there are more than five earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI.

2. If, with regard to the precautionary designation statement contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.

Continuation of Box IV:

BENASSI, John M.; BLAYLOCK, Richard L.; BUSH, Diana L.; DUFT, Bradford J.; GUISE, Jeffrey W.; HOSTETLER, Michael J.; HSU, Lee; KJELLAND, Kurt M.; KORNICZKY, Stephen S.; KREUSSER, Edward O.; MAHANEY, F.T. Alexandra; MCGEEHAN, Lisa M.; MILLER, Julia A.; MUNSON, Peter R.; MURDOCK, Douglas C.; NORTON, Vicki G.; OLSON, Douglas E.; PAGLIERY, Richard H.; PETERSON, John E.; PETTIT, Jonathan L.; UBELL, Franklin D.; WEINSTEIN, Peter D.; WEISER, Anatoly; WISNIA, Howard N.; and WOLFF, Jessica R. of Brobeck, Phleger & Harrison LLP, 12390 El Camino Real, San Diego, CA 92130

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Box No. VI PRIORITY CLAIM

The priority of the following earlier application(s) is hereby claimed:

Filing date of earlier application *(day/month/year)*	Number of earlier application	Where earlier application is:		
		national application: country	regional application:* regional Office	international application: receiving Office
item (1) (02.05.01) 02 May 2001	60/288,293	US		
item (2)				
item (3)				
item (4)				
item (5)				

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office)* identified above as:

☐ all items ☒ item (1) ☐ item (2) ☐ item (3) ☐ item (4) ☐ item (5) ☐ other, see Supplemental Box

* *Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii)):* . . . .

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)*:

ISA / US

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority)*:

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII DECLARATIONS

The following declarations are contained in Boxes Nos. VIII (i) to (v) *(mark the applicable check-boxes below and indicate in the right column the number of each type of declaration)*:		Number of declarations
☐ Box No. VIII (i)	Declaration as to the identity of the inventor	:
☐ Box No. VIII (ii)	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	:
☐ Box No. VIII (iii)	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	:
☐ Box No. VIII (iv)	Declaration of inventorship (only for the purposes of the designation of the United States of America)	:
☐ Box No. VIII (v)	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	:

Box No. IX CHECK LIST; LANGUAGE OF FILING 99

This international application contains:		This international application is accompanied by the following item(s) *(mark the applicable check-boxes below and indicate in right column the number of each item)*:	Number of items
(a) the following number of sheets in paper form:			
request (including declaration sheets)	6	1. ☒ fee calculation sheet	1
description (excluding sequence listing part)	9	2. ☐ original separate power of attorney	
claims	3	3. ☐ original general power of attorney	
abstract	1	4. ☐ copy of general power of attorney; reference number, if any:	
drawings	0	5. ☐ statement explaining lack of signature	
Sub-total number of sheets	19	6. ☐ priority document(s) identified in Box No. VI as item(s):	
sequence listing part of description *(actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (b) below)*		7. ☐ translation of international application into *(language)*:	
Total number of sheets	19	8. ☐ separate indications concerning deposited microorganism or other biological material	
(b) sequence listing part of description filed in computer readable form		9. ☐ sequence listing in computer readable form (indicate also type and number of carriers (diskette, CD-ROM, CD-R or other))	
(i) ☐ only (under Section 801(a)(i))		(i) ☐ copy submitted for the purposes of international search under Rule 13*ter* only (and not as part of the international application)	
(ii) ☐ in addition to being filed in paper form (under Section 801(a)(ii))		(ii) ☐ *(only where check-box (b)(i) or (b)(ii) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Rule 13*ter*	
Type and number of carriers (diskette, CD-ROM, CD-R or other) on which the sequence listing part is contained *(additional copies to be indicated under item 9(ii), in right column)*:		(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left column	
		10. ☒ other *(specify)*: Trans Ltr. & Return Postcard	2
Figure of the drawings which should accompany the abstract:		**Language of filing of the international application:** English	

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

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

Richard H. Pagliery

For receiving Office use only

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

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

This sheet is not part of and does not count as a sheet of the international application.

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PCT

FEE CALCULATION SHEET

Annex to the Request

For receiving Office use only

International Application No.

Date stamp of the receiving Office

Applicant's or agent's file reference: 30569.014.WO

Applicant: SICOR Inc.

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE . . . . . 240.00 [T]

2. SEARCH FEE . . . . . 700.00 [S]

International search to be carried out by ISA/US

(If two or more International Searching Authorities are competent to carry out the international search, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

Basic Fee

Where item (b) of Box No. IX applies, enter Sub-total number of sheets
Where item (b) of Box No. IX does not apply, enter Total number of sheets } 19

[b1] first 30 sheets . . . . . 407.00 [b1]

[b2] _____ (number of sheets in excess of 30) x _____ (fee per sheet) = _____ [b2]

[b3] additional component (only if sequence listing part of description is filed in computer readable form under Section 801(a)(i), or both in that form and on paper, under Section 801(a)(ii)):

400 x _____ (fee per sheet) = _____ [b3]

Add amounts entered at b1, b2 and b3 and enter total at B . . . . 407.00 [B]

Designation Fees

The international application contains 93 designations.

5 (number of designation fees payable *(maximum 5)*) x 88.00 (amount of designation fee) = 440.00 [D]

Add amounts entered at B and D and enter total at I . . . . . 847.00 [I]

(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.)

4. FEE FOR PRIORITY DOCUMENT *(if applicable)* . . . . . 15.00 [P]

5. TOTAL FEES PAYABLE . . . . . 1,802.00 TOTAL

Add amounts entered at T, S, I and P, and enter total in the TOTAL box

[X] The designation fees are not paid at this time.

MODE OF PAYMENT

[ ] authorization to charge deposit account (see below) [ ] postal money order [ ] cash [ ] coupons

[ ] cheque [ ] bank draft [ ] revenue stamps [ ] other *(specify)*:

AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT

(This mode of payment may not be available at all receiving Offices)

Receiving Office: RO/ US

Deposit Account No.: _____

[ ] Authorization to charge the total fees indicated above.

[ ] *(This check-box may be marked only if the conditions for deposit accounts of the receiving Office so permit)* Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.

[ ] Authorization to charge the fee for priority document.

Date: May 1, 2002

Name: Richard H. Pagliery

Signature: Richard H. Pagliery

See Notes to the fee calculation sheet

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
RICHARD H. PAGLIERY
BROBECK, PHLEGER & HARRISON LLP
12390 EI CAMINO REAL
SAN DIEGO, CA 92130

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

	Date of Mailing (*day/month/year*) 19 SEP 2002
Applicant's or agent's file reference 30569.014.WO	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US02/13801	International filing date (*day/month/year*) 01 May 2002 (01.05.2002)
Applicant SICOR INC.	

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 two months from the date of transmittal of the international search report.

   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. Reminders

   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 90 *bis*.1 and 90 *bis*.3, respectively, before the completion of the technical preparations for international publication.

   Within 19 months from the priority date, but only in respect of some designated Offices, 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); otherwise the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/US Commissioner for Patents Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Felicia D. Roberts for Cyrille Delacroix-Muirheid Telephone No. 703-308-1235

Form PCT/ISA/220 (April 2002) *(See notes on accompanying sheet)*

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 30569.014.WO	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/US02/13801	International filing date (*day/month/year*) 01 May 2002 (01.05.2002)	(Earliest) Priority Date (*day/month/year*) 02 May 2001 (02.05.2001)
Applicant SICOR INC.		

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 3 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 38.2(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. ☐ None of the figures
   ☐ because the applicant failed to suggest a figure.
   ☐ because this figure better characterizes the invention.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/13801

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61K 31/66
US CL : 514/107; 562/13
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)
U.S. : 514/107; 562/13

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
none

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6,160,165 A (SHINAL) 12 December 2000 (12.12.00), see entire document, especially column 1, lines 49-51; and column 2, lines 30-50.	1-19
Y,P	US 6,268,524 B1 (SHINAL) 31 July 2001 (31.07.01), see entire document.	1-19
Y,E	US 2002/0058647 A1 (HANDRECK et al) 16 May 2002 (16.05.02), see entire document.	1-19

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

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

"E" earlier application or patent 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 understand the principle or theory underlying the invention

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 August 2002 (15.08.2002)	19 SEP 2002
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Felicia D. Roberts for Cybille Delacroix-Muirheid Telephone No. 703-308-1235

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

PCT/US02/13801

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Continuation of B. FIELDS SEARCHED Item 3:
EAST:
pamidronate disodium, injection, intravenous, mannitol, acids, lactose, sucrose, sodium hydroxide

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
RICHARD H. PAGLIERY
BROBECK, PHLEGER & HARRISON LLP
12390 EL CAMINO REAL
SAN DIEGO, CA 92130

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

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Applicant's or agent's file reference 30569.014.WO	Date of Mailing *(day/month/year)* FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US02/13801	International filing date *(day/month/year)* 01 May 2002 (01.05.2002)
Applicant SICOR INC.	

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 two months from the date of transmittal of the international search report.

   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. **Reminders**

   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 90 *bis*.1 and 90 *bis*.3, respectively, before the completion of the technical preparations for international publication.

   Within 19 months from the priority date, but only in respect of some designated Offices, 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); otherwise the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/US Commissioner for Patents Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Felicia D. Roberts for Cyrille Delacroix-Muirheid Telephone No. 703-308-1235

Form PCT/ISA/220 (April 2002) *(See notes on accompanying sheet)*

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NOTES TO FORM PCT/ISA/220 (continued)

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 29, 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 claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under Article 19(1)" (Rule 46.4)

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.

The statement should be brief, it should not exceed 500 words if in English or if translated into English.

It should not be confounded 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 should 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.

In what language ?

The amendments must be made in the language in which the international application is published. The letter and any statement accompanying the amendments must be in the same language as the international application if that language is English or French; otherwise, it must be in English or French, at the choice of the applicant.

Consequence 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 62.2(a), first sentence).

Consequence 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/elected Offices, instead of, or in addition to, the translation of the claims as filed.

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

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty and of the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule" and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purpose of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended ?

The claims only.

The description and the drawings may only be amended during international preliminary examination under Chapter II.

When ? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments ?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How ? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

What documents must/may accompany the amendments ?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confounded with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

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.

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

PAGLIERY, Richard, H.
Brobeck, Phleger & Harrison, LLP
12390 El Camino Real
San Diego, CA 92130
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year) 08 July 2002 (08.07.02)	
Applicant's or agent's file reference 30569.014.WO	**IMPORTANT NOTIFICATION**
International application No. PCT/US02/13801	International filing date (day/month/year) 01 May 2002 (01.05.02)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 02 May 2001 (02.05.01)
Applicant SICOR INC. et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

4. The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
02 May 2001 (02.05.01)	60/288,293	US	04 June 2002 (04.06.02)

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

Facsimile No. (41-22) 740.14.35

Authorized officer

Jocelyn JEANNEROT

Telephone No. (41-22) 338.83.38

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/13801

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61K 31/66
US CL : 514/107; 562/13
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)
U.S. : 514/107; 562/13

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
none

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6,160,165 A (SHINAL) 12 December 2000 (12.12.00), see entire document, especially column 1, lines 49-51; and column 2, lines 30-50.	1-19
Y,P	US 6,268,524 B1 (SHINAL) 31 July 2001 (31.07.01), see entire document.	1-19
Y,E	US 2002/0058647 A1 (HANDRECK et al) 16 May 2002 (16.05.02), see entire document.	1-19

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

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

"E" earlier application or patent 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 understand the principle or theory underlying the invention

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 August 2002 (15.08.2002)	19 SEP 2002
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Cynthia Delacroix-Muirheid Telephone No. 703-308-1235

Form PCT/ISA/210 (second sheet) (July 1998)

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Continuation of B. FIELDS SEARCHED Item 3:
EAST:
pamidronate disodium, injection, intravenous, mannitol, acids, lactose, sucrose, sodium hydroxide

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54

SUPERINDUSTRIA Y COMERCIO
Radicacion : 03095881 00000000 Folios: 54
Fecha (AMD): 2003-10-28 16:22:19
Tramite : 011 PCT-PATENT 379 FASE NAC1 411 PRESENTAC
Dependencia: 2000 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

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

Firma Responsable:

Fecha:

Folios 56 y 57.
Extracto publicación

Industria y Comercio
SUPERINTENDENCIA

55 58

2020
Bogotá, D.C.,

Doctor:
RAMIRO CASTRO DUQUE
Apoderado
Sicor Inc.

Oficio N° 11180

ASUNTO:	Radicación N°	03-095881
	Solicitud internacional	PCT/US02/13801
	Fecha inicio fase nacional	02/12/2003
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

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

- La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486).
- La solicitud no contiene el poder debidamente otorgado, con el lleno de los 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 ésta fuere persona jurídica.

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

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

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

19 DIC. 2003

El anterior requerimiento fue notificado por fijación en lista de fecha_____.

208054