(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 May 2012 (24.05.2012)

WIPO | PCT

(10) International Publication Number
WO 2012/066492 A1

(51) International Patent Classification:
C07D 477/06 (2006.01) *A61K 31/407* (2006.01)

(21) International Application Number:
PCT/IB2011/055139

(22) International Filing Date:
16 November 2011 (16.11.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2724/DEL/2010 16 November 2010 (16.11.2010) IN

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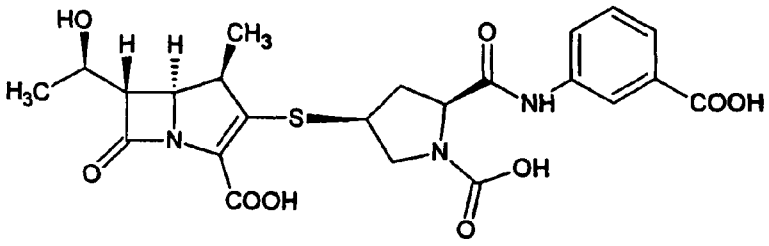
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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

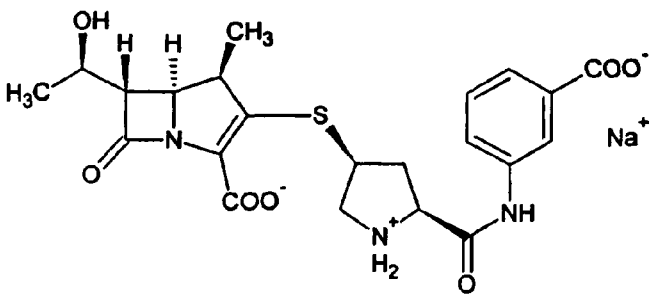
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH,

[Continued on next page]

(54) Title: PROCESSES FOR THE PREPARATION OF CARBAPENEM ANTIBIOTIC COMPOSITION



FORMULA II



FORMULA I

(57) Abstract: The present invention relates to processes for the preparation of carbapenem antibiotic compositions, involving the preparation of the compound of formula II from a compound of formula I and a composition comprising the compound of formula II. (I) (II).

WO 2012/066492 A1

GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

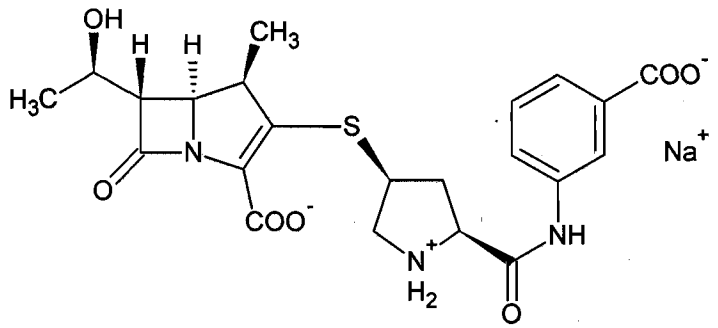
PROCESSES FOR THE PREPARATION OF CARBAPENEM ANTIBIOTIC COMPOSITION

Field of the Invention

The present invention relates to processes for the preparation of carbapenem antibiotic compositions.

Background of the Invention

Carbapenem antibiotics are widely used in treating infections caused by a broad range of pathogens including multi-drug-resistant bacteria. Ertapenem sodium is a carbapenem antibiotic, which is chemically 4*R*-[3(3*S**,5*S**),4α,5β,6β(*R**)]]-3-[[5-[[(3-carboxyphenyl)amino]carbonyl]-3-pyrrolidinyl]thio]-6-(1-hydroxyethyl)-4-methyl-7-oxo-1- azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid monosodium salt of Formula I.



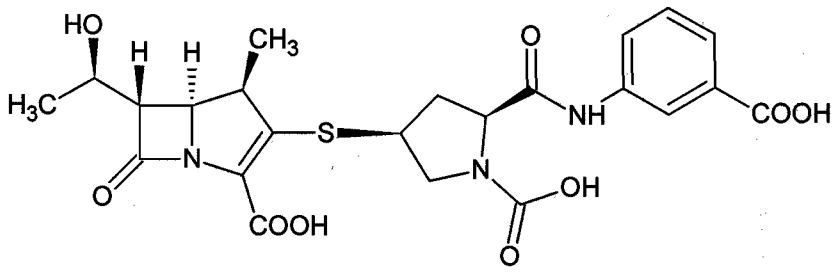
FORMULA I

Processes for the preparation of ertapenem sodium are provided in U.S. Patent No. 5,652,233 and *J. Org. Chem.*, 70, p. 7479-7487 (2005). U.S. Patent No. 7,022,841 provides a process for preparing ertapenem sodium of Formula I as crystalline Form A, Form B and Form C. U.S. Patent No. 7,022,841 also provides a process for reducing residual solvents from Form A, Form B and Form C by sweeping nitrogen through the wet solid at low temperature conditions and by employing agitated filter dryers.

U.S. Patent No. 6,548,492 discloses that ertapenem sodium of Formula I is sensitive to temperature and pH fluctuations and remains unstable at temperatures above about -20°C. U.S. Patent No. 6,548,492 further discloses that ertapenem sodium undergoes dimerization and hydrolysis to form undesirable dimers and ring-opened compounds above about -20°C. *J. Liq. Chrom. & Rel. Technol.*, 24(19), p. 2999-3015

(2001), provides for the preparation, isolation and associated characterization data of the degradation impurities of ertapenem sodium.

As stated in U.S. Patent No. 5,952,323, when ertapenem or its sodium salts are formulated in a pharmaceutical composition with a suitable amount of sodium carbonate or sodium bicarbonate, the compound of Formula II or sodium salts are formed upon dilution or reconstitution.



FORMULA II

U.S. Patent No. 6,548,492 describes a vial lyophilization process for the preparation of a pharmaceutical composition that includes a compound of Formula II or its salts. According to said process, a sterile aqueous solution containing the compound of Formula II or its salts is prepared, filled in vials, lyophilized under specific lyophilization conditions, and the vials are removed as final formulation. The initial sterile aqueous solution containing the compound of Formula II or its salts is prepared by adding an effective amount of a molar ratio of ertapenem sodium of Formula I and a base into a reaction vessel containing the aqueous solution of a carbon dioxide source; maintaining a pH of about 6.0 to about 9.0 and a temperature range of about -3°C to about 15°C.

However, the lyophilized product obtained according to the process described in U.S. Patent No. 6,548,492 has a purity of only about 95% and contains more than 2% of ring opening impurities. Further, dimer impurities are present in the lyophilized product in a range of 1.5% to 1.6% in a lab scale batch and increases to more than 2% at the pilot plant scale batch level.

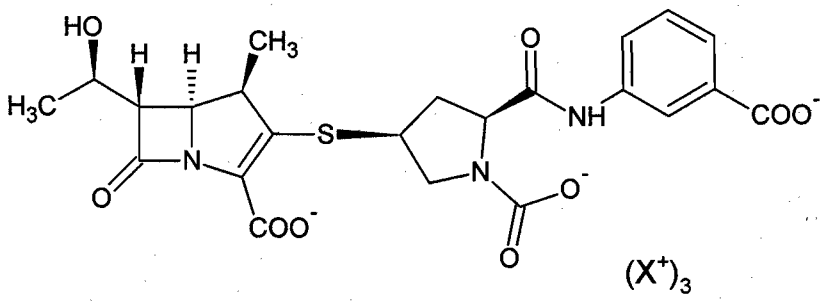
WO 2009/150630 describes a tray lyophilization process of a sterile aqueous solution containing the compound of Formula II, or its salts. The tray lyophilization method described provides a process to obtain the carbapenem antibiotic composition with increased purity levels. The initial sterile aqueous solution containing the compound of Formula II or its salts is prepared by simultaneous addition of ertapenem sodium of

Formula I and a base into a reaction vessel containing the aqueous solution of carbon dioxide source.

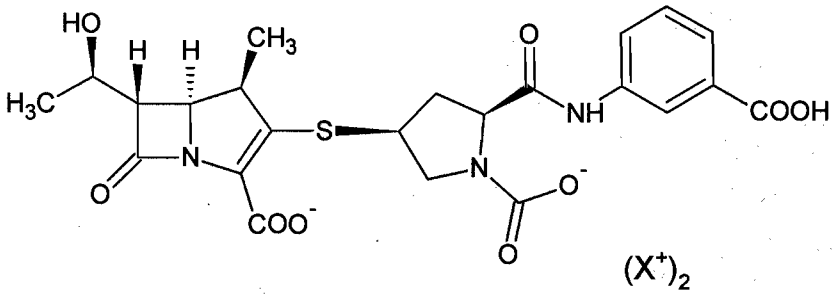
Summary of the Invention

The present inventors have found that a composition that includes the compound of Formula II or its salts can be prepared with total impurity content less than about 3.5% w/w and any individual impurity content less than about 2% w/w by modifying the sequence of addition of ertapenem sodium of Formula I, the carbon dioxide source and the base while preparing the aqueous solution containing the compound of Formula II or its salts. The present process provides a way to achieve improved purity levels even with vial lyophilization in comparison with the purity levels reported in the prior art for vial lyophilization. The present process is suitable for preparing the composition comprising the compound of Formula II or its salts at industrial scale.

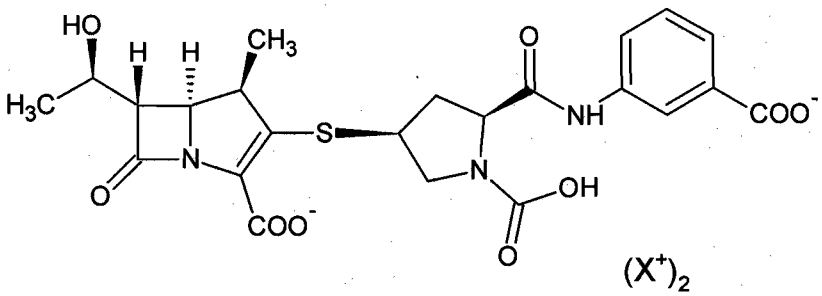
The salts of the compound of Formula II, for example, alkali metal salts, according to the present invention may exist in various ionization states and their combinations, depending on the carbon dioxide source and the base used for preparing the composition. The compounds of Formula IIa through IIg are examples of the alkali metal salt forms of the compound of Formula II.



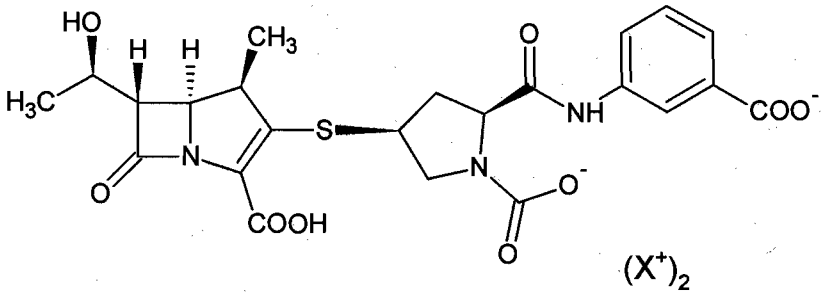
FORMULA IIa



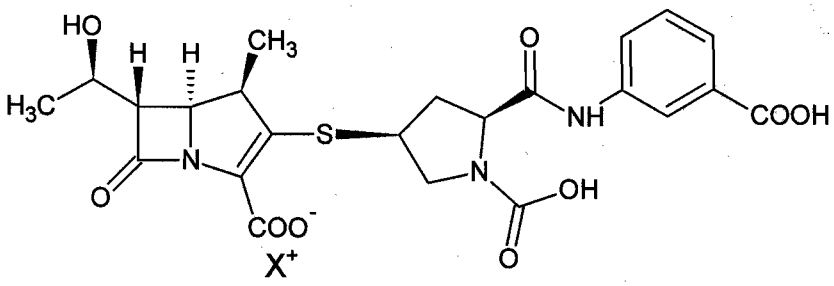
FORMULA IIb



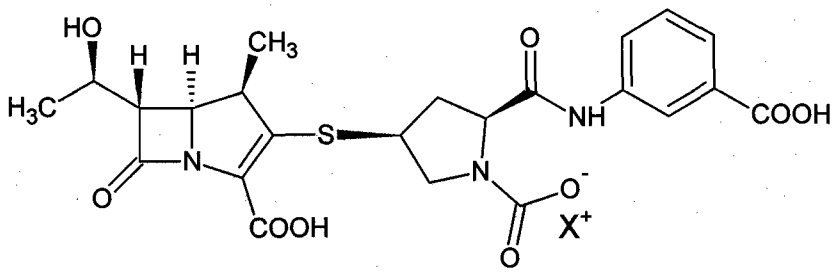
FORMULA IIc



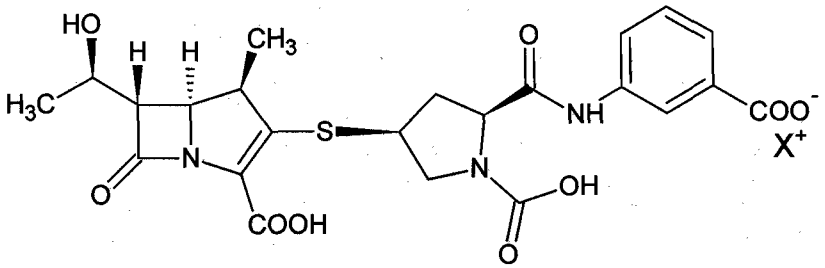
FORMULA IId



FORMULA IIe



FORMULA IIf

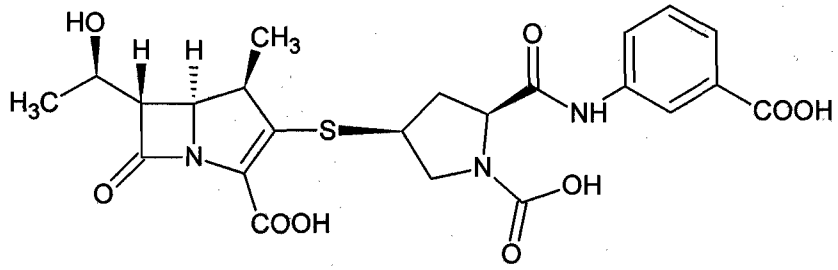


FORMULA IIg

wherein X is an alkali metal, for example, sodium or potassium.

Detailed Description of the Invention

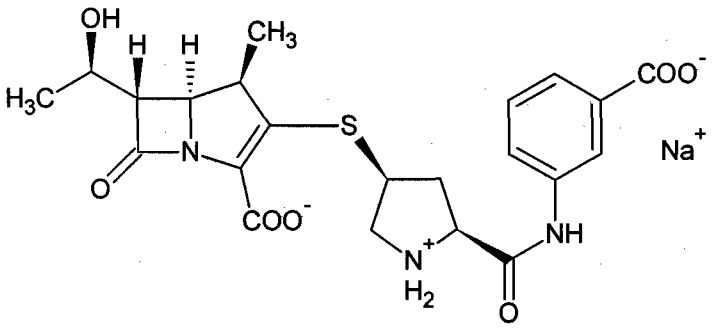
The present invention provides a process for the preparation of a composition comprising the compound of Formula II, or its salts;



FORMULA II

wherein the process includes:

a) adding a mixture of ertapenem sodium of Formula I and a carbon dioxide source to water into a compounder or adding water to a mixture of ertapenem sodium of Formula I and a carbon dioxide source into a compounder to obtain a solution;



FORMULA I

b) treating the solution obtained in step a) with a base while maintaining the pH at about 6.5 to about 8.5; and

c) lyophilizing the solution obtained in step b) in a lyophilizer to obtain a composition comprising the compound of Formula II or its salts.

The ertapenem sodium of Formula I used as the starting material may be prepared according to the methods provided in WO 2009/150630. A mixture of ertapenem sodium of Formula I and the carbon dioxide source is added to water into a compounder or water is added to a mixture of ertapenem sodium of Formula I and a carbon dioxide source into a compounder to obtain a solution.

The compounder may be a vessel, for example, a stainless steel jacketed vessel. The addition may be carried out at a temperature range of about -5°C to about 15°C, for example, about 0°C to about 10°C. The carbon dioxide source may be selected from the group of alkali metal carbonates, alkali metal bicarbonates, alkaline earth metal carbonates and alkaline earth metal bicarbonates.

The carbon dioxide source may be, for example, sodium bicarbonate or sodium carbonate. The mixture of ertapenem sodium of Formula I and carbon dioxide source may be a solid or a semisolid mixture.

The water may be United States Pharmacopeia (USP). The water may be used in a quantity sufficient to dissolve ertapenem sodium of Formula I and the carbon dioxide source.

The dissolution may be facilitated by stirring. The solution so obtained is treated with a base while maintaining a pH at about 6.5 to about 8.5. The pH may be maintained between about 7.4 to about 7.7 during said treatment. The pH may be maintained in said

range by a sequential addition of the base as an aqueous solution. The treatment with base may be carried out at a temperature range of about -5°C to about 15°C, for example, about 0°C to about 10°C.

The base may be an inorganic base or an organic base. The base may be selected from a group of alkali hydrides, alkali hydroxides, alkaline hydroxides, alkali carbonates and amines. The base may be, for example, sodium hydroxide. The volume of the solution may optionally be increased to a specified batch size or volume with further addition of water. The solution so obtained is optionally filtered through an about 0.2 micron membrane filter to obtain a sterile solution.

The solution is subsequently lyophilized in a lyophilizer. The lyophilization method may be vial lyophilization or tray lyophilization. In case of vial lyophilization, a suitable quantity of the solution that includes the compound of Formula II or its salts so obtained is filled in the vials and partially sealed. In case of tray lyophilization, the solution that includes the compound of Formula II or its salts is transferred to a lyophilization tray. Conventional lyophilization trays including steel, aluminum, glass, plastic or Lyoguard® trays may be employed. Total mass and tray thickness may be suitably optimized.

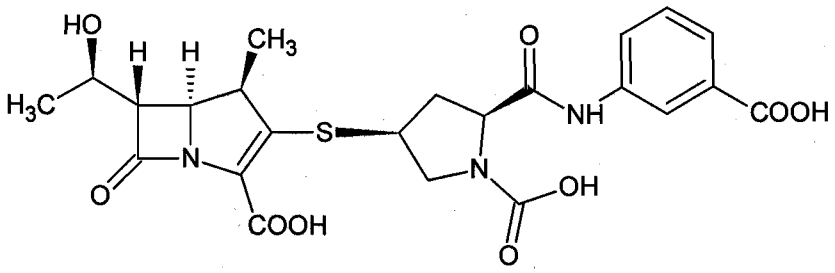
The lyophilization process may be carried out by freezing the solution that includes the compound of Formula II or its salts at a temperature of about -40°C or below, for example, about -50°C to about -45°C to obtain a frozen composition. The primary drying of the frozen composition may be carried out at a temperature of about -35°C to about 0°C for up to about 60 hours. The secondary drying may be carried out at a temperature of about 10°C to about 65°C. The secondary drying may be carried out for up to about 40 hours. The entire drying process may be carried out under pressure of up to about 150 mTorr, for example, about 75 mTorr to about 150 mTorr.

The lyophilized composition that includes the compound of Formula II or its salts so obtained has total impurity content less than about 3.5% w/w and any individual impurity content less than about 2% w/w. The lyophilized composition that includes the compound of Formula II or its salts is unloaded from the lyophilizer.

In case of vial lyophilization, the vials containing the composition so obtained may be completely sealed under a partial vacuum after lyophilization. In case of tray

lyophilization, the composition so obtained may be packed suitably in containers including, for example, vials.

The present invention also provides for a process for the preparation of a composition that includes the compound of Formula II, or its salts;



FORMULA II

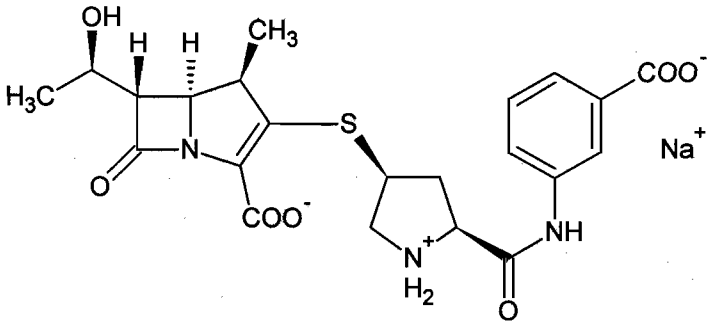
wherein the process includes:

a) adding ertapenem sodium of Formula I, a carbon dioxide source, and water simultaneously or in optional order of succession into a compounder to obtain a solution;

adding a solution of ertapenem sodium of Formula I in water and a carbon dioxide source simultaneously or in optional order of succession into a compounder to obtain a solution; or

adding ertapenem sodium of Formula I and a solution of carbon dioxide source in water simultaneously or in optional order of succession into a compounder to obtain a solution;

with the proviso that ertapenem sodium of Formula I is not added into a compounder which contains only an aqueous solution of a carbon dioxide source.



FORMULA I

b) treating the solution obtained in step a) with a base while maintaining a pH at about 6.5 to about 8.5; and

c) lyophilizing the solution obtained in step b) in a lyophilizer to obtain a composition comprising the compound of Formula II or its salts.

The ertapenem sodium of Formula I used as the starting material may be prepared according to the methods provided in WO 2009/150630. The ertapenem sodium of Formula I, a carbon dioxide source and water are added simultaneously or in optional order of succession, including simultaneous addition of any two of ertapenem sodium of Formula I, a carbon dioxide source and water, into a compounder to obtain a solution; or a solution of ertapenem sodium of Formula I and a carbon dioxide source are added simultaneously or in optional order of succession into a compounder to obtain a solution; or ertapenem sodium of Formula I and a solution of carbon dioxide source in water are added simultaneously or in optional order of succession into a compounder to obtain a solution; with the proviso that ertapenem sodium of Formula I is not added into a compounder which contains only an aqueous solution of a carbon dioxide source.

The compounder may be a vessel, for example, a stainless steel jacketed vessel. The addition may be carried out at a temperature range of about -5°C to about 15°C, for example, about 0°C to about 10°C.

The carbon dioxide source may be selected from the group of alkali metal carbonates, alkali metal bicarbonates, alkaline earth metal carbonates and alkaline earth metal bicarbonates. The carbon dioxide source may be, for example, sodium bicarbonate or sodium carbonate.

The water may be water for injection, United States Pharmacopeia (USP). The water may be used in a quantity sufficient to dissolve ertapenem sodium of Formula I and the carbon dioxide source.

The dissolution may be facilitated by stirring. The solution so obtained is treated with a base while maintaining a pH at about 6.5 to about 8.5. The pH may be maintained, for example, between about 7.4 to about 7.7 during said treatment.

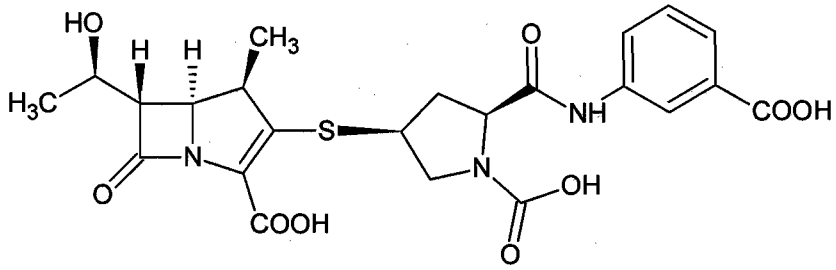
The pH may be maintained in said range, for example, by a sequential addition of the base as an aqueous solution. The treatment with base may be carried out at a temperature range of about -5°C to about 15°C, for example, about 0°C to about 10°C.

The base may be an inorganic base or an organic base. The base may be selected from the group of alkali hydrides, alkali hydroxides, alkaline hydroxides, alkali carbonates and amines. The base may be, for example, sodium hydroxide. The volume of the solution may optionally be increased to a specified batch size or volume with further addition of water. The solution so obtained is optionally filtered through an about 0.2 micron membrane filter to obtain a sterile solution.

The solution is subsequently lyophilized in a lyophilizer. The lyophilization method may be vial lyophilization or tray lyophilization. In case of vial lyophilization, a suitable quantity of the solution that includes the compound of Formula II or its salts so obtained is filled in the vials and partially sealed. In case of tray lyophilization, the solution that includes the compound of Formula II or its salts is transferred to a lyophilization tray. Conventional lyophilization trays including steel, aluminum, glass, plastic or Lyoguard® trays may be employed. Total mass and tray thickness may be suitably optimized.

The lyophilization process may be carried out by freezing the solution that includes the compound of Formula II or its salts at a temperature of about -40°C or below, for example, about -50°C to about -45°C to obtain a frozen composition. The primary drying of the frozen composition may be carried out at a temperature of about -35°C to about 0°C for up to about 60 hours. The secondary drying may be carried out at a temperature of about 10°C to about 65°C. The secondary drying may be carried out for up to about 40 hours. The entire drying process may be carried out under pressure of up to about 150 mTorr, for example, about 75 mTorr to about 150 mTorr. The lyophilized composition that includes the compound of Formula II or its salts so obtained has total impurity content less than about 3.5% w/w and any individual impurity content less than about 2% w/w. The lyophilized composition that includes the compound of Formula II or its salts is unloaded from the lyophilizer. In case of vial lyophilization, the vials containing the composition so obtained may be completely sealed under a partial vacuum after lyophilization. In case of tray lyophilization, the composition so obtained may be packed suitably in containers including, for example, vials.

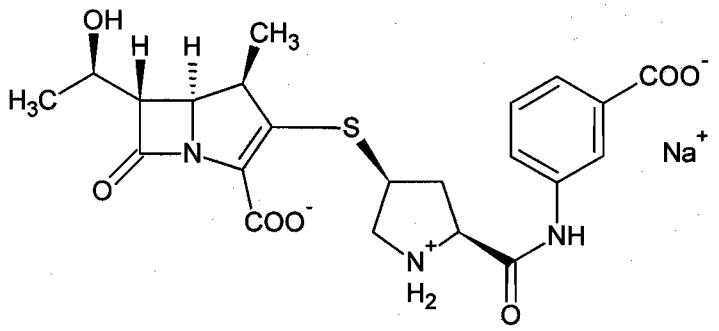
The present invention also provides a process for the preparation of a composition comprising the compound of Formula II or its salts;



FORMULA II

wherein the process includes:

a) adding ertapenem sodium of Formula I or its solution in water, a carbon dioxide source or its solution in water, and an aqueous base simultaneously or in optional order of succession into a compounder to obtain a solution, with the proviso that ertapenem sodium of Formula I is not added into a compounder which contains only an aqueous solution of a carbon dioxide source;



FORMULA I

b) optionally adjusting the pH of the solution obtained in step a) to about 6.5 to about 8.5; and

c) lyophilizing the solution obtained in step b) in a lyophilizer to obtain a composition comprising the compound of Formula II, or its salts.

The ertapenem sodium of Formula I used as the starting material may be prepared according to the methods provided in WO 2009/150630. The ertapenem sodium of Formula I or its solution in water, a carbon dioxide source or its solution in water and an aqueous base are added simultaneously or in optional order of succession, including simultaneous addition of any two of ertapenem sodium of Formula I or its solution in water, a carbon dioxide source or its solution in water, and water, into a compounder to

obtain a solution with the proviso that ertapenem sodium of Formula I is not added into a compounder which contains only an aqueous solution of a carbon dioxide source. The compounder may be a vessel, for example, a stainless steel jacketed vessel. The addition may be carried out at a temperature range of about -5°C to about 15°C, for example, about 0°C to about 10°C.

The carbon dioxide source may be selected from the group of alkali metal carbonates, alkali metal bicarbonates, alkaline earth metal carbonates and alkaline earth metal bicarbonates. The carbon dioxide source may be sodium bicarbonate or sodium carbonate.

The base may be an inorganic base or an organic base. The base may be selected from the group of alkali hydrides, alkali hydroxides, alkaline hydroxides, alkali carbonates and amines. The base may be sodium hydroxide.

The aqueous solution of the base may be prepared by treating the base with water. The water may be water for injection, United States Pharmacopeia (USP). The water may be used in a quantity sufficient to dissolve ertapenem sodium of Formula I, the carbon dioxide source and the base.

The dissolution may be facilitated by stirring. The pH of the solution so obtained may be optionally adjusted to a pH at about 6.5 to about 8.5. The pH may be adjusted, for example, between about 7.4 to about 7.7. The pH may be adjusted to said range, for example, by the addition of a base or an acid depending on the initial pH. The pH adjustment may be carried out at a temperature range of about -5°C to about 15°C, for example, about 0°C to about 10°C. The volume of the solution may optionally be increased to a specified batch size or volume with further addition of water. The solution so obtained is optionally filtered through an about 0.2 micron membrane filter to obtain a sterile solution.

The solution is subsequently lyophilized in a lyophilizer. The lyophilization method may be vial lyophilization or tray lyophilization. In the case of vial lyophilization, a suitable quantity of the solution that includes the compound of Formula II or its salts so obtained is filled in the vials and partially sealed. In case of tray lyophilization, the solution that includes the compound of Formula II or its salts is transferred to a lyophilization tray. Conventional lyophilization trays including steel, aluminum, glass,

plastic or Lyoguard® trays may be employed. Total mass and tray thickness may be suitably optimized.

The lyophilization process may be carried out by freezing the solution that includes the compound of Formula II or its salts at a temperature of about -40°C or below, for example, about -50° to about -45°C, to obtain a frozen composition. The primary drying of the frozen composition may be carried out at a temperature of about -35°C to about 0°C for up to about 60 hours. The secondary drying may be carried out at a temperature of about 10°C to about 65°C. The secondary drying may be carried out for up to about 40 hours. The entire drying process may be carried out under pressure of up to about 150 mTorr, for example, about 50 mTorr to about 150 mTorr.

The lyophilized composition that includes the compound of Formula II or its salts so obtained has total impurity content less than about 3.5% w/w and any individual impurity content less than about 2% w/w. The lyophilized composition that includes the compound of Formula II or its salts is unloaded from the lyophilizer.

In case of vial lyophilization, the vials containing the composition so obtained may be completely sealed under a partial vacuum after lyophilization. In case of tray lyophilization, the composition so obtained may be packed suitably in containers including, for example, vials.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

EXAMPLES

Example 1: Preparation of a Carbapenem Antibiotic Composition

Water for injection, USP (400 mL) was cooled to 2°C to 8°C in a stainless steel jacketed vessel (2 L) and nitrogen was purged continuously into the vessel. A solid mixture of ertapenem sodium (135.2 g) and sodium bicarbonate (17.5 g) was added into the vessel and stirred until a clear solution was obtained. The pH of the solution was adjusted to 7.5 with sodium hydroxide solution (5.0% w/v, 5 ml). Water for injection, USP (40 mL) was added to the solution to attain a batch volume of 600 mL and filtered through a 0.2 micron membrane filter. The filtered solution (6 mL) was filled into

individual glass vials (100 vials of 23 mL capacity). The glass vials were partially sealed with dry stoppers and lyophilized according to the conditions provided below:

STEP	STEP TYPE	TEMPERATURE (°C)	VACUUM (mTorr)	TIME (min)
Vials loaded at -5°C to -10°C				
1	Freezing	-10°C	---	5
2	Freezing	-25°C	---	25
3	Freezing	-50°C	---	60
4	Freezing	-50°C	---	120
5	Evacuation	---	500	10
6	Drying	-30°C	150	120
7	Drying	-30°C	150	600
8	Drying	-20°C	80	120
9	Drying	-20°C	80	1250
10	Drying	-10°C	80	60
11	Drying	-10°C	80	1050
12	Drying	0°C	80	120
13	Drying	0°C	80	300
14	Drying	30°C	80	60
15	Drying	30°C	80	300
16	Drying	45°C	50	60
17	Drying	45°C	50	180
18	Post heat	25°C	50	30
Secondary Set point : 60°C Condenser Temperature : -75°C Extra Freeze : -50°C for 10 minutes				
Total Time				4480

The vials were sealed under vacuum (50 mmHg) at a temperature of 25°C.

Moisture content: 1.25% w/w

Assay: 1105.27 mg/vial

Total impurity content: 2.985% w/w

Any individual impurity (highest): 1.794% w/w

Example 2: Preparation of a Carbapenem Antibiotic Composition

Water for injection, USP (400 mL) was cooled to 2°C to 8°C in a stainless steel jacketed vessel (2 L) and nitrogen was purged continuously into the vessel. A solid ertapenem sodium (135.2 g) was added into the vessel and stirred until a clear solution was obtained. Sodium bicarbonate (17.5 g) was added to the vessel and stirred until a clear solution was obtained. The pH of the solution was adjusted to 7.5 with sodium hydroxide

solution (5.0% w/v, 5 mL). Water for injection, USP (40 mL) was added to the solution to attain a batch volume of 600 mL and filtered through a 0.2 micron membrane filter. The filtered solution (6 mL) was filled into individual glass vials (100 vials of 23 mL). The glass vials were partially sealed with dry stoppers and lyophilized according to the conditions provided below:

STEP	STEP TYPE	TEMPERATURE (°C)	VACUUM (mTorr)	TIME (min)
Vials loaded at -5°C to -10°C				
1	Freezing	-10°C	---	5
2	Freezing	-25°C	---	25
3	Freezing	-50°C	---	60
4	Freezing	-50°C	---	120
5	Evacuation	---	500	10
6	Drying	-30°C	150	120
7	Drying	-30°C	150	600
8	Drying	-20°C	80	120
9	Drying	-20°C	80	1250
10	Drying	-10°C	80	60
11	Drying	-10°C	80	1050
12	Drying	0°C	80	120
13	Drying	0°C	80	300
14	Drying	30°C	80	60
15	Drying	30°C	80	300
16	Drying	45°C	50	60
17	Drying	45°C	50	180
18	Post heat	25°C	50	30
Secondary Set Point : 60°C Condenser Temperature : -75°C Extra Freeze : -50°C for 10 minutes				
Total Time				4480

The vials were sealed under vacuum (50 mmHg) at a temperature of 25°C.

Moisture content: 1.28% w/w

Assay: 1151.23 mg/vial

Total impurity content: 3.140% w/w

Any individual impurity (highest): 1.681% w/w

Example 3: Preparation of a Carbapenem Antibiotic Composition

Water for injection, USP (400 mL) was cooled to 2°C to 8°C in a stainless steel jacketed vessel (2 L) and nitrogen was purged continuously into the vessel. Sodium

hydroxide (5.0% w/v) and solid ertapenem sodium (135.2 g) were added into the vessel and stirred until a clear solution was obtained. The sodium bicarbonate (17.5 g) was added to the vessel and stirred until a clear solution was obtained. The pH of the solution was adjusted to 7.5 with sodium hydroxide solution (5.0% w/v). Water for injection, USP (40 mL) was added to the solution to attain a batch volume of 600 mL and filtered through a 0.2 micron membrane filter. The filtered solution (6 mL) was filled into individual glass vials (100 vials of 23 mL). The glass vials were partially sealed with dry stoppers and lyophilized according to the conditions provided below:

STEP	STEP TYPE	TEMPERATURE (^{0}C)	VACUUM (mTorr)	TIME (min)
Vials loaded at -5°C to -10°C				
1	Freezing	-10°C	---	5
2	Freezing	-25°C	---	25
3	Freezing	-50°C	---	60
4	Freezing	-50°C	---	120
5	Evacuation	---	500	10
6	Drying	-30°C	150	120
7	Drying	-30°C	150	600
8	Drying	-20°C	80	120
9	Drying	-20°C	80	1250
10	Drying	-10°C	80	60
11	Drying	-10°C	80	1050
12	Drying	0°C	80	120
13	Drying	0°C	80	300
14	Drying	30°C	80	60
15	Drying	30°C	80	300
16	Drying	45°C	50	60
17	Drying	45°C	50	180
18	Post heat	25°C	50	30
Secondary Set point : 60°C Condenser Temperature : -75°C Extra Freeze : -50°C for 10 minutes				
Total Time				4480

The vials were sealed under vacuum (50 mmHg) at a temperature of 25°C.

Moisture content: 1.5% w/w

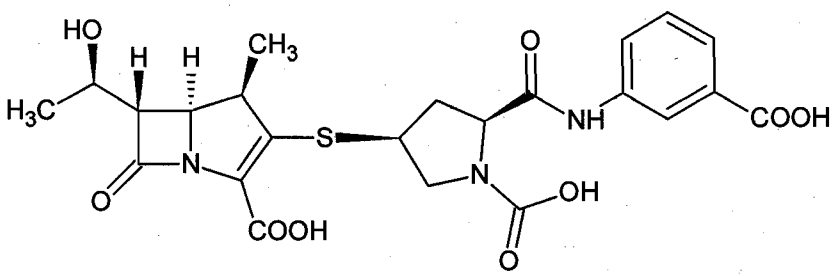
Assay: 1112.53 mg/vial

Total impurity content: 3.012% w/w

Any individual impurity (highest): 1.756% w/w

We Claim:

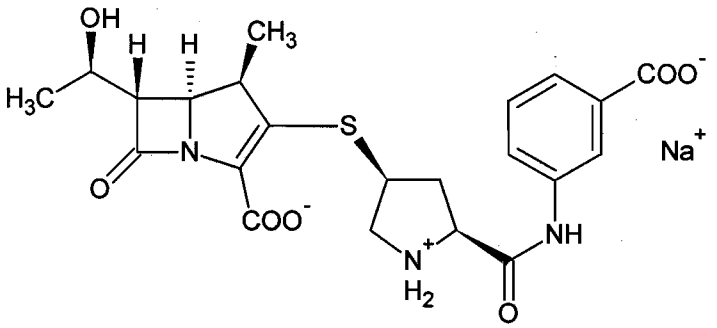
1. A process for the preparation of a composition comprising the compound of Formula II or its salts;



FORMULA II

wherein the process comprises:

a) adding a mixture of ertapenem sodium of Formula I and a carbon dioxide source to water into a compounder or adding water to a mixture of ertapenem sodium of Formula I and a carbon dioxide source into a compounder to obtain a solution;

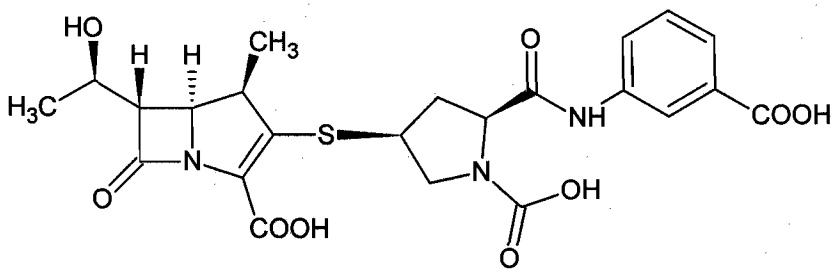


FORMULA I

b) treating the solution obtained in step a) with a base while maintaining a pH at about 6.5 to about 8.5; and

c) lyophilizing the solution obtained in step b) in a lyophilizer to obtain a composition comprising the compound of Formula II, or its salts.

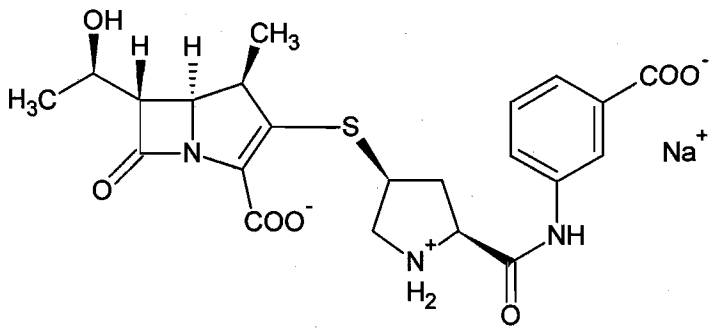
2. A process for the preparation of a composition comprising the compound of Formula II or its salts;



FORMULA II

wherein the process comprises:

a) adding ertapenem sodium of Formula I, a carbon dioxide source, and water simultaneously or in optional order of succession into a compounder to obtain a solution; adding a solution of ertapenem sodium of Formula I in water and a carbon dioxide source simultaneously or in optional order of succession into a compounder to obtain a solution; or adding ertapenem sodium of Formula I and a solution of carbon dioxide source in water simultaneously or in optional order of succession into a compounder to obtain a solution, with the proviso that ertapenem sodium of Formula I is not added into a compounder which contains only an aqueous solution of a carbon dioxide source;

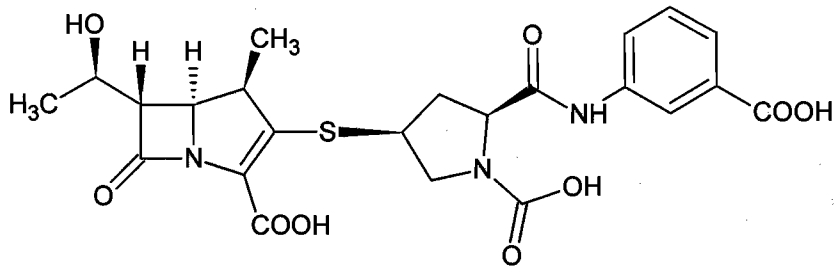


FORMULA I

b) treating the solution obtained in step a) with a base while maintaining a pH at about 6.5 to about 8.5; and

c) lyophilizing the solution obtained in step b) in a lyophilizer to obtain a composition comprising the compound of Formula II, or its salts.

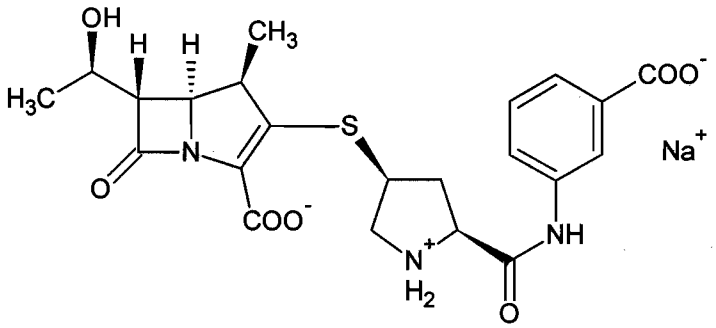
3. A process for the preparation of a composition comprising the compound of Formula II, or its salts;



FORMULA II

wherein the process comprises:

a) adding ertapenem sodium of Formula I or its solution in water, a carbon dioxide source or its solution in water, and an aqueous base simultaneously or in optional order of succession into a compounder to obtain a solution, with the proviso that ertapenem sodium of Formula I is not added into a compounder which contains only an aqueous solution of a carbon dioxide source;



FORMULA I

b) optionally adjusting the pH of the solution obtained in step a) to about 6.5 to about 8.5; and

c) lyophilizing the solution obtained in step b) in a lyophilizer to obtain a composition comprising the compound of Formula II, or its salts.

4. A process according to claims 1, 2 or 3, wherein step a) is carried out at a temperature range of about -5°C to about 15°C.

5. A process according to claims 1, 2 or 3, wherein the carbon dioxide source comprises sodium bicarbonate or sodium carbonate.

6. A process according to claims 1, 2 or 3, wherein step b) is carried out at a temperature of about -5°C to about 15°C.

7. A process according to claims 1, 2 or 3, wherein the base comprises sodium hydroxide.

8. The lyophilized composition of claims 1, 2 or 3 has total impurity content less than about 3.5% w/w and any individual impurity content less than about 2% w/w.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2011/055139

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D477/06 A61K31/407
ADD.

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)
C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 548 492 B1 (AL-DEHNEH ANTHONY [US] ET AL) 15 April 2003 (2003-04-15) cited in the application	1-8
Y	claims 15-22; examples 1-4	1-7
Y	US 5 952 323 A (ZIMMERMAN JEFFREY A [US] ET AL) 14 September 1999 (1999-09-14) cited in the application column 2, line 52 - column 3, line 40	1-7
X	WO 2009/150630 A2 (RANBAXY LAB LTD [IN]; GEORGE VINOD [IN]; VASHISHTA BHUPENDRA [IN]; PRA) 17 December 2009 (2009-12-17) cited in the application page 14, line 16 - page 15, line 25; claims 12-17; example 2	1-8

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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

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

"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
7 March 2012	20/03/2012

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Grassi, Damian

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2011/055139

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WILLIAMS J M ET AL: "Practical Synthesis of the New Carbapenem Antibiotic Ertapenem Sodium", JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY, EASTON.; US, vol. 70, no. 19, 16 September 2005 (2005-09-16), pages 7479-7487, XP002591997, ISSN: 0022-3263, DOI: 10.1021/JO0501442 [retrieved on 2005-08-13] cited in the application figure 2	8
X	& WILLIAMS J M ET AL: "Supporting Information. Practical Synthesis of the New Carbapenem Antibiotic Ertapenem Sodium", JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY, EASTON.; US, vol. 70, no. 19, 16 September 2005 (2005-09-16), page S1-S4, ISSN: 0022-3263, DOI: 10.1021/JO0501442 [retrieved on 2005-08-13] S2: preparation of the lyophilized composition comprising compound 8	8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2011/055139

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☒ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 8(completely); 1-7(partially)

   Process according to claim 1 involving the addition of a mixture of ertapenem sodium and a carbon dioxide source.

   ---

2. claims: 1-7(partially)

   Process according to claim 1 involving the addition of water to a mixture of ertapenem sodium and a carbon dioxide source.

   ---

3. claims: 2-7(partially)

   Process according to claim 2 involving the addition of ertapenem sodium, a carbon dioxide source and water simultaneously or in optional order of succession (the group is still not unitary).

   ---

4. claims: 2-7(partially)

   Process according to claim 2 involving the addition of a solution of ertapenem sodium in water and a carbon dioxide source simultaneously or in optional order of succession.

   ---

5. claims: 2-7(partially)

   Process according to claim 2 involving the addition of ertapenem sodium and a solution of a carbon dioxide source in water simultaneously or in optional order of succession.

   ---

6. claims: 3-7(partially)

   Processes according to claim 3 (the group is still not unitary).

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2011/055139

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6548492 B1	15-04-2003	US 6548492 B1	15-04-2003
		US 2002002160 A1	03-01-2002
US 5952323 A	14-09-1999	NONE	
WO 2009150630 A2	17-12-2009	EP 2303225 A2	06-04-2011
		US 2011172201 A1	14-07-2011
		WO 2009150630 A2	17-12-2009