Title: HIGHLY PURE CEFIDITOREN PIVOXIL.

Abstract: The present invention relates to a highly pure cefditoren pivoxil having purity above about 98.5% and total impurity content less than about 3.0% when measured by HPLC.
HIGHERLY PURE CEFITOREN PIVOXIL

Field of the Invention

The present invention relates to a highly pure cefditoren pivoxil having purity above about 98.5% and total impurity content less than about 3.0% when measured by HPLC.

Background of the Invention

[6R-[3(Z),6α,7β(Z)]-7-[[2-Amino-4-thiazolyl](methoxyimino)acetyl]amino]-3-[2-(4-methyl-5-thiazolyl)ethenyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-carboxylic acid, pivaloyloxyethyl ester, commonly known as cefditoren pivoxil of Formula I is ester prodrug of cefditoren.

FORMULA I

It is a third generation cephalosporin derivative belonging to the class of 3-(2-substituted vinyl) cephalosporin described in European Patent No 175610. Cefditoren pivoxil is highly active not only against a variety of gram-positive and gram-negative bacteria but also against some resistant strains of bacteria.

European Patent No 175 610 describes a process for the preparation of an amorphous form of cefditoren pivoxil. The process described is non-selective and gives more than 20% of the unwanted E-isomer, which must then be separated, for example, by column chromatography. The purity of cefditoren pivoxil obtained is typically about
94.0% to about 95.5% when analyzed by HPLC. The product obtained typically has total impurities in excess of about 4.5%.

U.S. Patent No. 6,294,669 describes a crystalline cefditoren pivoxil and a process for preparing the same. The crystalline substance described has a purity of about 97 to 98%, typically 97.7%, which is still not sufficiently pure to incorporate it in a pharmaceutical composition. The total impurities present in the crystalline material so prepared are in excess of about 4.5% when measured by an HPLC assay as set forth, for example, in U.S. Patent No. 6,441,162.

U.S. Patent No 6,288,223 describes a process for the selective preparation of Z-isomer of 3-(2-substituted vinyl)cephalosporins. The process described uses stringent conditions for the deprotection of amino and carboxyl functionalities. The process isolates and purifies each intermediate, and therefore is very time consuming, and gives a low yield of Cefditoren pivoxil. In addition to this, the total impurity content in cefditoren pivoxil prepared as per the method disclosed in the ‘223 Patent is found to be in excess of about 4.5% when measured by HPLC.

U.S. Patent No 5,616,703 describes a process for separation of cephalosporin isomers by forming amine salts. The process described therein produces intermediates in which the unwanted E-isomer is present at levels of more than 20%. The E-isomer is then depleted by forming amine salts. In this process the yield of the intermediate is reduced and the unwanted E-isomer is thrown away after separation. The patent however, does not provide a synthesis of cefditoren pivoxil.

Impurities which are commonly present in cefditoren pivoxil are ceftamet pivoxil of Formula II, $\Delta^2$-isomer of Formula III, E-isomer of Formula IV, Anti-isomer of Formula V, N-Pivolamide of Formula VI, Dimer-1252 of Formula VII and Dimer-1367. Several unknown impurities may also be commonly observed.
FORMULA II

FORMULA III

FORMULA IV

FORMULA V
Summary of the Invention

It has been found that cefditoren pivoxil can be obtained in high purity of above about 98.5% having less than about 3% of total impurities when measured by HPLC.

The term highly pure cefditoren pivoxil refers to cefditoren pivoxil in amorphous or crystalline form having purity not less than about 98.5% containing less than about 3.0% of total impurities. More preferably the purity is not less than 99.0% which has less than about 2.0% total impurities. Most preferably highly pure cefditoren pivoxil refers to cefditoren pivoxil having purity not less than about 99.20% containing less than about 1.5% of total impurities. The purity expression whenever referred in the specification means as determined by HPLC.

Detailed Description of the Invention

In a first aspect herein provides a highly pure cefditoren pivoxil having purity greater than about 98.5% containing less than about 3.0% of total impurities. More preferably the present invention provides highly pure cefditoren pivoxil having purity
greater than about 99.0% containing less than about 2.0% of total impurities. Most preferably the present invention provides highly pure cefditoren pivoxil having purity greater than about 99.2% containing less than about 1.5% of total impurities.

In a further aspect, herein is provided highly pure cefditoren pivoxil having less than about 0.5% of ceftamet pivoxil of Formula II. More preferably ceftamet pivoxil impurity is less than about 0.3%.

In another aspect, herein is provided highly pure cefditoren pivoxil having less than about 1.0% of $\Delta^2$-isomer of Formula III, preferably less than about 0.75% and most preferably less than about 0.5%. The percentage of $\Delta^2$-isomer of Formula III in cefditoren pivoxil increases upon storage for extended period. It is therefore believed important to limit the presence of the $\Delta^2$-isomer in the final product at an early stage.

In yet another aspect, herein is provided highly pure cefditoren pivoxil having less than about 0.1% of N-Pivolamide of Formula VI. More preferably N-Pivolamide is less than about 0.05% and most preferably N-Pivolamide is less than detectable quantity.

In still another aspect, herein is provided highly pure cefditoren pivoxil having less than about 0.85% of Dimer-1252 of Formula VII.

In yet a further aspect, herein is provided highly pure cefditoren pivoxil having less than 0.75% of Dimer-1367.

In yet another aspect, herein is provided a process for preparation of highly pure cefditoren pivoxil wherein the process comprises:

a) crystallizing cefditoren pivoxil from a mixture of C$_{3-10}$ ketone and C$_{1-4}$ alkanol; and

b) isolating highly pure cefditoren pivoxil from the reaction mass thereof.

Cefditoren pivoxil can be prepared, for example, according to the process described in Indian Patent Application No. 1004/DEL/2003. The material is added to a mixture of C$_{3-10}$ ketone and C$_{1-4}$ alkanol. The resultant mass is allowed to stir at a temperature of from about -20 to about 100°C to complete crystallization. The material is then isolated from the reaction mass by conventional methods used in cephalosporin chemistry known to a person of ordinary skills to obtain highly pure cefditoren pivoxil.
having purity above about 98.5% and total impurities less than about 3.0%. Highly pure cefditoren pivoxil obtained contains less than 0.5% of ceftamet pivoxil of Formula II, less than 0.1% (for example, not a detectable amount) of N-Pivolamide of Formula VI, less than 0.85% of Dimer-1252 of Formula VII and less than 0.75% of Dimer-1367.

C$_{1,4}$ alkanols can be selected from, for example, methanol, ethanol, isopropyl alcohol, n-butanol, isobutanol or tert-butanol. C$_{3,10}$ ketone can be selected from, for example, acetone, ethyl methyl ketone, diisobutyl ketone, methyl isobutyl ketone and methyl tert-butyl ketone.

Crystallization temperatures can be, for example, between about 0 and about 60°C.

The isolated cefditoren pivoxil is then optionally dried under vacuum to get highly pure cefditoren pivoxil.

In still a further aspect, herein is provided a process for preparation of highly pure amorphous form cefditoren pivoxil wherein the process comprises:

a) crystallizing cefditoren pivoxil from a mixture of C$_{3,10}$ ketone and C$_{1,4}$ alkanol;

b) isolating highly pure cefditoren from the reaction mass thereof;

c) dissolving highly pure cefditoren pivoxil in a suitable organic solvent;

d) adding a second organic solvent to the solution or solution to the second organic solvent in optional order of succession in order to precipitate cefditoren pivoxil; and

e) isolating highly pure amorphous cefditoren pivoxil from the reaction mass.

Highly pure cefditoren pivoxil can be dissolved in first organic solvent selected from, for example, water-immiscible or partially miscible solvents such as iso-butanol, n-butanol, ethyl formate, methyl acetate, ethyl acetate, butyl acetate, isobutyl acetate, methyl ethyl ketone, diisobutyl ketone, methyl isobutyl ketone, methylene chloride, ethylene chloride, chloroform or mixtures thereof and to the solution added second organic solvent selected from, for example, diisopropyl ether, diethyl ether, toluene, xylene, heptane, hexane, cyclohexane, cycloheptane, petroleum ether or mixtures thereof in optional order of succession to affect the precipitation of cefditoren pivoxil from the reaction mass. To enhance the precipitation, common techniques such as seeding with amorphous material or cooling the reaction mass can also be effectively performed. The precipitated product is
then isolated from the reaction mass and then optionally dried under vacuum to get highly pure amorphous form of cefditoren pivoxil.

The dissolution of highly pure cefditoren pivoxil in the first organic solvent can be effected conveniently by initially dissolving crystalline cefditoren pivoxil in a third organic solvent selected from, for example, dimethylformamide, dimethylacetamide, tetrahydrofuran, 1,4-dioxane, methanol, acetone, acetonitrile, ethanol, isopropanol or mixtures thereof. To this solution are added water and a first organic solvent in optional order of succession, to obtain a biphasic solution. The organic layer is then separated and may be washed successively with water to remove the traces of the third organic solvent.

A solution of highly pure cefditoren pivoxil in the first organic solvent can thus be effectively prepared.

In yet a further aspect, herein is provided a process for the preparation of a highly pure amorphous form of cefditoren pivoxil wherein the process comprises:

a) dissolving highly pure cefditoren pivoxil in suitable organic solvent;

b) removing the solvent from the reaction mass; and

c) isolating a highly pure amorphous form of cefditoren pivoxil.

The suitable organic solvent is already described as the first organic solvent above. If required, optional heating can be carried out to dissolve the crystalline form completely in the organic solvent(s). The dissolution of crystalline cefditoren pivoxil in the suitable organic solvent can be affected by the method described above.

Concentration of solvent can be carried out under vacuum of about 100 to 0.01 mm of Hg wherein the solvent is removed by vacuum distillation of the solution with optionally heating the solution at a temperature of about 0 to 100°C to effect faster removal of the solvent.

The solvent can also be removed by spray-drying the solution of crystalline cefditoren pivoxil using a spray-dryer. For the purpose of spray-drying, a mini-spray Dryer (Model: Buchi 190 Switzerland) which operates on the principle of nozzle spraying in a parallel - flow i.e. the sprayed product and the drying gas flow in the same direction, was used. The drying gas can be air or inert gases such as nitrogen, argon or carbon dioxide.
In another aspect, herein are provided pharmaceutical compositions comprising highly pure cefditoren pivoxil optionally containing a pharmaceutically acceptable carrier.

In a further aspect, herein is provided a method of treating infections caused by Gram-positive, Gram-negative and resistant strains of bacteria which comprises administering to a mammalian host in need thereof a therapeutically effective amount of the highly pure cefditoren pivoxil.

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 included within the scope of the present invention.

**HPLC Parameters:**
- Column: C\textsubscript{18} column, 5 μ, 150 mm x 4.6 mm
- Mobile Phase: Phosphate Buffer (pH 4.5), gradient with methanol and phosphate buffer (pH 4.5)
- Flow Rate: 1.5 ml per minute
- UV Detector: 245 nm.

**Example 1: Preparation of Cefditoren Pivoxil**

To a stirred mixture of N,N-dimethylformamide (28 Lt.) and Cefditoren sodium (2.8 Kg) at -18 to -20°C was added 2,2-Dimethylpropionic acid iodomethyl ester (1.4 Kg) in one lot. The temperature of the reaction mass was maintained at -20 to -15°C for 90 minutes. The resultant mixture was poured into a pre-cooled (0 - 5 °C) mixture of ethyl acetate (84 Lit) and deionized water (56 Lit) at 5 - 10°C. The layers were separated and the organic layer was washed twice with aqueous sodium bisulphite solution (2.5% w/v, 28 Lit) at ambient temperature. Finally the resultant organic layer was washed with deionized water (28 Lit).

The organic layer was treated with activated carbon (0.28 Kg) at 20 - 25°C for 30 - 40 minutes and the resultant mixture was filtered through celite bed. The filtrate was concentrated to remove ethyl acetate under vacuum (20 - 25 mm) at 35 - 40°C till the ratio of solids to solvent is about 1:4. Slowly added the above residue to cyclohexane (84
Lit) under stirring at 25 – 30°C in 25 minutes and further stirred for 30 minutes at 25 – 30°C. The separated solids were filtered and washed with cyclohexane (2 x 8.4 Lit). The solids were then dried under vacuum at 40 – 45°C for about 12 to 18 hours to get title compound in a Yield of 2.60 Kg (92%).

Example 2: Preparation Of Highly Pure Cefditoren Pivoxil

To the product obtained in Example 1 (2.5 Kg) was added denatured spirit (20 Lit) and the mass was stirred for 2 hours at 25 – 30°C. The separated solids were filtered and wash with denatured spirit (5 Lit) and suck dried. To the wet solids were added a mixture of methanol (25 Lit) and acetone (25 Lit). The resultant mixture was stirred at 20 – 25°C to get a clear solution. The resultant solution was concentrated under vacuum at 25 – 30°C to about 3 - 4 times of the residue volume against input quantity. The mass was further cooled to 5°C and stirred at 5 – 10°C for 2 hours. The product was filtered and washed cold (0 -5°C) acetone (2.5 Lit) and dried under vacuum at 40 – 45°C to get highly pure cefditoren pivoxil in a Yield of 1.82 Kg (72%), having the following impurity profile: Ceftamet pivoxil: 0.29%; $\Delta^2$-isomer: 0.09%; E-isomer: 0.10%; Anti-isomer: 0.09%; N-pivalomide: not detectable; Dimer-1252: 0.44%; Dimer-1367: 0.09%.

Example 3: Preparation Of Highly Pure Amorphous Cefditoren Pivoxil

Highly pure cefditoren pivoxil (2.0 g) was dissolved in dimethylformamide (10 ml) at ambient temperature. This solution was added to pre-cooled ethyl acetate at 0 – 5°C. Solution was washed with water in three times. Ethyl acetate was concentrated under reduced pressure to get a solution of Cefditoren pivoxil about 250 mg / ml. This solution was added to cyclohexane (60 ml) slowly in 10 – 15 min at ambient temperature and stirred for 60 min. Solid was filtered to get title compound in a Yield of 1.79 gm, with the following impurity profile: Ceftamet pivoxil: 0.31%; $\Delta^2$-isomer: 0.08%; E-isomer: 0.10%; Anti-isomer: 0.08%; N-pivalomide: not detectable; Dimer-1252: 0.46%; Dimer-1367: 0.09%.
Example 4: Preparation Of Amorphous Cefditoren Pivoxil From Crystalline Cefditoren Pivoxil

Crystalline Cefditoren pivoxil (20.0 g) was dissolved in DMF (100 ml) at ambient temperature. This solution was added to pre-cooled mixture of ethyl acetate (600 ml) and water (400 ml) at 5 – 10°C. Resultant mixture was stirred for 10 to 15 minutes and the layers were separated. The solution was subjected to spray-drying using a mini spray-dryer (Buchi Model 190) at an inlet temperature of 75°C and outlet temperature of 55°C with a feed rate of 15 ml per minute. Cefditoren pivoxil (15 g) was thus obtained in an amorphous form, having the following impurity profile: Ceftamet pivoxil: 0.31%; Δ²-isomer: 0.08%; E-isomer: 0.10%; Anti-isomer: 0.08%; N-pivalomide: not detectable; Dimer-1252: 0.46%; Dimer-1367: 0.09%.
WE CLAIM:

1. Highly pure cefditoren pivoxil having purity greater than about 98.5% and total impurities less than about 3%.

2. Highly pure cefditoren pivoxil as claimed in claim 1, wherein purity is greater than about 99.0% and total impurities are less than about 2.0%.

3. Highly pure cefditoren pivoxil as claimed in claim 2, wherein purity is greater than about 99.2% and total impurities are less than about 1.5%.

4. Highly pure cefditoren pivoxil as claimed in claim 1, having less than about 0.5% of ceftamet pivoxil of Formula II.

![Formula II]

FORMULA II

5. Highly pure cefditoren pivoxil as claimed in claim 4, wherein ceftamet pivoxil is less than about 0.3%.

6. Highly pure cefditoren pivoxil as claimed in claim 1, having less than about 1.0% of $\Delta^2$-isomer of Formula III.

![Formula III]

FORMULA III

7. Highly pure cefditoren pivoxil as claimed in claim 6, wherein $\Delta^2$-isomer is less than about 0.75%.
8. Highly pure cefditoren pivoxil as claimed in claim 7, wherein \( \Delta^2 \)-isomer is less than about 0.5%.

9. Highly pure cefditoren pivoxil as claimed in claim 1, having less than 0.1% of N-Pivolamide of Formula VI.

\[ \text{Formula VI} \]

10. Highly pure cefditoren pivoxil as claimed in claim 9, wherein N-Pivolamide is not detectable.

11. Highly pure cefditoren pivoxil as claimed in claim 1, having less than about 0.85% of Dimer-1252 of Formula VII.

\[ \text{Formula VII} \]

12. Highly pure cefditoren pivoxil as claimed in claim 1, having less than about 0.75% of Dimer-1367.

13. A process for preparation of highly pure cefditoren pivoxil, wherein the process comprises

   a) crystallizing cefditoren pivoxil from a mixture of \( C_{3-10} \) ketone and \( C_{1-4} \) alkanol; and

   b) isolating highly pure cefditoren pivoxil from the reaction mass thereof.
14. A process as claimed in claim 13, wherein step a) is carried at a temperature of about -20 to about 100°C.

15. A process as claimed in claim 14, wherein step a) is carried at a temperature of about 0 to about 60°C.

16. A process as claimed in claim 13, wherein C\textsubscript{1-4} alkanol is selected from methanol, ethanol, isopropyl alcohol, n-butanol, isobutanol and tert-butanol.

17. A process as claimed in claim 13, wherein C\textsubscript{3-10} ketone is selected from acetone, ethyl methyl ketone, diisobutyl ketone, methyl isobutyl ketone and methyl tert-butyl ketone.

18. A process for preparation of highly pure amorphous form cefditoren pivoxil, wherein the process comprises

   a) crystallizing cefditoren pivoxil from a mixture of C\textsubscript{3-10} ketone and C\textsubscript{1-4} alkanol;
   b) isolating highly pure cefditoren from the reaction mass thereof;
   c) dissolving highly pure cefditoren pivoxil in a first organic solvent;
   d) adding a second organic solvent to the solution or solution to the second organic solvent in optional order of succession in order to precipitate cefditoren pivoxil; and
   e) isolating highly pure amorphous cefditoren pivoxil from the reaction mass.

19. A process as claimed in claim 18, wherein the first organic solvent is selected from water-immiscible or partially miscible solvents.

20. A process as claimed in claim 19, wherein the first organic solvent is selected from iso-butanol, n-butanol, ethyl formate, methyl acetate, ethyl acetate, butyl acetate, isobutyl acetate, methyl ethyl ketone, diisobutyl ketone, methyl isobutyl ketone, methylene chloride, ethylene chloride and chloroform.

21. A process as claimed in claim 18, wherein the second organic solvent is selected from diisopropyl ether, diethyl ether, toluene, xylene, heptane, hexane, cyclohexane, cycloheptane and petroleum ether.

22. A process for preparation of highly pure amorphous form of cefditoren pivoxil wherein the process comprises
a) dissolving highly pure cefditoren pivoxil in an organic solvent;

b) removing the solvent from the reaction mass; and

c) isolating highly pure amorphous form of cefditoren pivoxil.

23. A process as claimed in claim 22, wherein the organic solvent is selected from isobutanol, n-butanol, ethyl formate, methyl acetate, ethyl acetate, butyl acetate, isobutyl acetate, methyl ethyl ketone, diisobutyl ketone, methyl isobutyl ketone, methylene chloride, ethylene chloride and chloroform.

24. A process as claimed in claim 22, wherein the solvent is removed by vacuum distillation.

25. A process as claimed in claim 22, wherein the solvent is removed by spray-drying.

26. A pharmaceutical composition comprising highly pure cefditoren pivoxil optionally containing a pharmaceutically acceptable carrier.

27. A method of treating infections caused by Gram-positive, Gram-negative and resistant strains of bacteria wherein the method comprises administering to a mammalian host in need thereof a therapeutically effective amount of highly pure cefditoren pivoxil.
## INTERNAL SEARCH REPORT

**PCT/IB2005/001988**

### A. CLASSIFICATION OF SUBJECT MATTER

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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)

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

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

- EPO–Internal
- WPI Data
- CHEM ABS Data

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>WO 98/12200 A (MEIJI SEIKA KAISHA LTD; YASUI, KIYOSHI; ONODERA, MASAIRO; SUKEGAWA, M) 26 March 1998 (1998-03-26) the whole document</td>
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Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents:

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

* "I" 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 novel or 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

* "F" document member of the same patent family

Date of the actual completion of the international search: 24 October 2005

Date of mailing of the international search report: 31/10/2005

Name and mailing address of the ISA:

European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk
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Authorized officer:

Von Daacke, A
### Box 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. [X] Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
   
   Although claim 27 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

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

### Box 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:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

- [ ] The additional search fees were accompanied by the applicant's protest.
- [ ] No protest accompanied the payment of additional search fees.
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WO 2005003141 A 13-01-2005 NONE

WO 2005044824 A 19-05-2005 NONE