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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 November 2011 (17.11.2011)

PCT

(10) International Publication Number
WO 2011/142730 A1

(51) International Patent Classification:
A61K 9/00 (2006.01) *A61K 31/545* (2006.01)

(21) International Application Number:
PCT/TR2011/000119

(22) International Filing Date:
2 May 2011 (02.05.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2010/03855 14 May 2010 (14.05.2010) TR

(72) Inventor; and
(71) Applicant : **BILGIC, Mahmut** [TR/TR]; Tozkoparan Mah. General Ali Riza Gurcan Cad. Merter Is, Merkezi Bagimsiz Bolum No:2/13 Merter/Istanbul, 34173 (TR).

(74) Agent: **KOSE, Meliha, Merve**; Tozkoparan Mah. General Ali Riza Gurcan Cad. Merter Is, Merkezi Bagimsiz Bolum No:2/13 Merter/Istanbul, 34173 (TR).

(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, RO, RS, RU, 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, GM, KE, LR, LS, MW, MZ, NA, 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))*

WO 2011/142730 A1

(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING CEFIXIME AND CLAVULANIC ACID DERIVATIVE COMPOUND

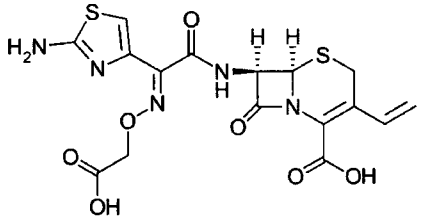
(57) Abstract: The present invention relates to pharmaceutical compositions comprising clavulanic acid and/or its derivatives with cefixime as the active agents.

PHARMACEUTICAL COMPOSITION COMPRISING CEFIXIME AND CLAVULANIC ACID DERIVATIVE COMPOUND

The present invention relates to pharmaceutical compositions comprising clavulanic acid and/or its derivatives with cefixime as the active agents.

Background of the Invention:

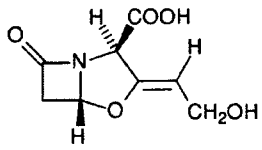
The substance which was first described in the European patent numbered EP0030630 (B1) and which is known as (6*R*,7*R*)-7-{[2-(2-amino-1,3-thiazol-4-yl)-2-(carboxy methoxyimino)acetyl]amino}-3-ethenyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid or "cefixime" (Formula 1) has been defined as a third generation cephalosporin and it is specified that it is indicated in the treatment of the infections caused by gram positive and gram negative bacteria.



Formula 1

Cefixime, which is in the form of a white or light yellow crystal powder, easily dissolves in methanol and propylene glycol while it partially dissolves in ethanol and acetone, and barely dissolves in ether, ethyl acetate, hexane and water. Its solubility in aqueous solutions, on the other hand, varies according to the pH value.

Clavulanic acid is a beta-lactamase inhibitor illustrated in Formula 2.



Formula 2

Clavulanic acid and derivatives thereof (for instance its salts such as potassium clavulanate) are known as the beta-lactamase inhibitors which withstand the beta-lactamase-originated resistance mechanism by suppressing the activity of beta-lactamase enzymes.

The patent numbered EP0593573 comprises a formulation relating to suspension forms of beta-lactam antibiotics and beta lactamase.

However, suspension forms are not preferred much as they have the potential of high and/or uncontrolled dose intake; there appear problems in their physical and chemical stability and they cause problems in use and carrying.

To this end, the inventors have aimed to develop stable oral pharmaceutical formulations which comprise cefixime and clavulanic acid derivatives together and eliminate the low solubility problem of cefixime.

Description of the Invention

The subject of the present invention relates to effervescent tablets and granules comprising cefixime and clavulanic acid derivative combinations and the procedures for their preparation. The effervescent tablets and granules pertaining to the present invention are packed in single dose packs, and therefore uncontrolled dose intake by the patients is prevented. Surprisingly, it was found that the effervescent tablet and granules comprising the active agent cefixime which are formulated according to the present invention entirely dissolve in water and form a homogeneous solution. Said pharmaceutical composition is characterized in comprising 5-20% cefixime in proportion to the total weight of the unit dose. It was unexpectedly observed that the pharmaceutical compositions comprising 5-20% cefixime with respect to the total unit dose weight dissolve in water without the need of any other disintegrant.

In one aspect, the present invention is characterized in that the amount of cefixime in the pharmaceutical composition comprising cefixime and cluvulanic acid in a combined form is in the range of 5-20%.

Cefixime, which can be used in effervescent tablet and granule formulations pertaining to the present invention, can be in the form of its solvates, hydrates, esters, enantiomers, racemates, organic salts, inorganic salts, polymorphs, crystal and amorphous forms or in free form and/or a combination thereof.

Cefixime to be used in scope of the present invention can be in any of the monohydrate, dihydrate, trihydrate and/or anhydrate forms. Preferably, cefixime trihydrate is used in the formulations pertaining to the present invention.

Cluvulanic acid, which can be used in the formulations pertaining to the present invention, can be in the form of its solvates, hydrates, enantiomers, racemates, organic salts, inorganic salts, polymorphs, crystal and amorphous forms or in free form and/or a combination thereof. Preferably, potassium clavulanate is used in scope of the present invention.

Another aspect of the present invention is the pharmaceutically composition comprising pharmaceutically acceptable excipients along with the active agents cefixime and potassium clavulanate.

Various excipients selected from, but not limited to, a group comprising glidants, lubricants, sweeteners, binders, flavoring agents, coloring agents and effervescent couple can be used in the formulation pertaining to the present invention apart from cefixime and potassium clavulanate.

The glidant which can be used in the formulation pertaining to the present invention can be selected from, but not limited to, a group comprising magnesium silicate, silicon dioxide, starch, talc, tribasic calcium phosphate or a combination thereof.

The lubricant pertaining to the present invention can be selected from, but not limited to, a group comprising calcium stearate, magnesium stearate, polyethylene glycol, PEG 6000, polyvinyl alcohol, potassium benzoate, talc, sodium benzoate. Preferably, PEG 6000 is used as the lubricant in the pharmaceutical composition pertaining to the present invention.

The sweetener that can be used in the pharmaceutical composition according to the present invention can be selected from a group comprising acesulfame, aspartame, fructose, maltitol, maltose, xylitol, saccharine, sodium cyclamate, sucralose, sucrose. Preferably, aspartame is used as the sweetener in the present invention.

The effervescent couple that can be used in the pharmaceutical composition pertaining to the present invention can be selected from organic acids such as citric acid, tartaric acid, malic acid, fumaric acid etc. and basic agents such as sodium hydrogen carbonate, sodium carbonate, potassium carbonate and potassium hydrogen carbonate etc. Preferably, citric acid and sodium hydrogen carbonate are used in the present invention.

It is known that cluvulanic acid and its derivatives used in the formulations pertaining to the present invention undergo degradation catalysed by acids and/or bases. To this respect, the ratio of the effervescent couple to be used to each other plays an important role on the

stability of clavulanic acid and its derivatives in the formulation. The inventors have observed that clavulanic acid is stable in the pharmaceutical compositions in the case that the ratio of effervescent acid to effervescent base used in the present invention is in the range of 5:1 to 1:1, preferably in the range of 2:1 to 1.1:1, most preferably in the range of 1.5:1 to 1.1:1.

According to this, another aspect of the present invention is effervescent tablet and granule formulations comprising cefixime and clavulanic acid or a combination of derivatives thereof wherein the ratio of the effervescent acid to the effervescent base is in the range of 5:1 to 1:1, preferably in the range of 2:1 to 1.1:1, most preferably in the range of 1.5:1 to 1.1:1.

The binder that can be used in the tablet and granule formulations pertaining to the present invention can be selected from a group comprising ethyl cellulose, gelatine, hypromellose, magnesium aluminum silicate, maltodextrin, polyethylene oxide and povidone. Preferably, povidone is used in the present invention.

It has been observed that the amount of the binder used in the formulation is significant for the obtained granule to be able to turn into tablets when desired and for the product that is turned into tablets to disperse in water in shorter than 5 minutes during the formulation of effervescent tablets and granules pertaining to the present invention. In consequence of the studies conducted, it has been observed that the granules can easily be turned into tablets and the tablets can dissolve in water in shorter than 5 minutes in the case that the ratio of cefixime to the binder is in the range of 10:1 to 1:1, preferably in the range of 6:1 to 3:1 in the pharmaceutical formulations prepared in accordance with the present invention.

According to this, another aspect of the present invention is effervescent tablet and granule formulations comprising cefixime and clavulanic acid or derivatives thereof wherein the ratio of cefixime to the binder is in the range of 10:1 to 1:1, preferably in the range of 6:1 to 3:1.

In the pharmaceutical composition according to the present invention, 20-800 mg cefixime or its pharmaceutically acceptable salts, hydrates, solvates or combinations thereof in an amount equal to this can be used.

In the pharmaceutical composition according to the present invention, 50-500 mg clavulanic acid or its pharmaceutically acceptable salts, hydrates, solvates or combinations thereof on an amount equal to this can be used.

Clavulanic acid and its derivatives (for instance, potassium clavulanate) are extremely sensitive to moisture. Therefore, potassium clavulanate is preferably used with a humectant in the ratio of 1:1 in the present invention.

One or more of the substances comprising silica; colloidal silica, for instance colloidal silica anhydrous, for example Aerosil® 200, magnesium trisilicate, cellulose powder, Cabosil®, magnesium oxide, calcium silicate, Syloid®, starch, microcrystalline cellulose, talc can be used as the humectant.

In the pharmaceutical composition pertaining to the present invention, potassium clavulanate is preferably used with microcrystalline cellulose or syloid in the ratio of 1:1, most preferably with syloid.

The amount of cefixime or its pharmaceutically acceptable solvates, hydrates, enantiomers, racemates, organic salts, inorganic salts, polymorphs, crystal or amorphous forms that the pharmaceutical composition pertaining to the present invention can comprise is in the range of 5-20%, preferably in the range of 8-15% with respect to the total weight of the unit dose.

The amount of clavulanic acid or its pharmaceutically acceptable salts, hydrates, solvates or a combination thereof in an equal amount to it that can be used in the pharmaceutical composition pertaining to the present invention is in the range of 5-50% with respect to the total weight of the unit dose.

The pharmaceutical composition pertaining to the present invention can comprise 5-20 % cefixime; 5-50% potassium clavulanate; 0-5% glidant; 0.1-5% lubricant; 0-5% binder; 20-90% effervescent couple; 0,1-10% sweetener; 0.1-5% flavoring agent; 0.1-5% coloring agent with respect to the total amount of the unit dose.

In another aspect, the pharmaceutical composition comprising cefixime and clavulanic acid or its derivatives which is prepared according to the present invention can be in effervescent tablet or granule form.

According to another aspect, the present invention relates to the processes which can be used for the preparation of pharmaceutical compositions comprising pharmaceutically acceptable excipients in addition to cefixime and clavulanic acid as the active agents.

The process pertaining to the present invention comprises granulation of the active agents cefixime and/or clavulanic acid or its derivatives through conventional wet and/or dry

granulation methods, or mixing cefixime, clavulanic acid derivatives and the other excipients through dry blending method, then powderizing them; and optionally compressing the mixture in tablet form.

Clavulanic acid undergoes degradation when it contacts with water, which leads to problems in the production of the products especially in granule form. Therefore, the inventors have developed a method which provides to formulate clavulanic acid without contacting water for producing the pharmaceutical compositions pertaining to the present invention.

According to this, the said process comprises the granulation of cefixime, the binder, the effervescent couple and the sweetener with an aqueous solution; drying the granules; mixing the obtained granules with clavulanic acid and/or its derivative, the coloring agent, the flavoring agent and the lubricant, and optionally compressing tablets in the tablet compressing machine.

In another aspect, the present invention relates to the use of the pharmaceutical composition in the production of a medicament so as to be used in the treatment of gram positive and gram negative bacteria.

According to another aspect of the present invention, the pharmaceutical composition prepared according to the present invention is used in the manufacture of a medicament so as to be used in upper respiratory infections such as ear, nose, throat, otitis media, sinusitis, tonsillitis, pharyngitis; lower respiratory tract infections such as pyelonephritis, cystitis and urethritis; skin or soft tissue infections such as froncle, pyoderma, impetigo; in the treatment and prophylaxis of gonorrhea and lyme diseases.

The pharmaceutical composition pertaining to the present invention can be prepared as described below, but not limited to the examples given.

EXAMPLE 1: Formulation for the preparation of film-coated tablet comprising cefixime and potassium clavulanate

	% of amount present in unit dose
Cefixime	10%
Potassium Clavulanate:Syloid	15%
Sweetener	3%
Effervescent Couple	65%
Binder	3%
Lubricant	1%
Flavoring Agent	1%
Coloring Agent	2%

CLAIMS:

1. A pharmaceutical composition comprising cefixime and clavulanic acid and/or derivatives thereof in a combined form characterized in that said composition comprises 5-20% cefixime.
2. The pharmaceutical composition according to claim 1, wherein said composition is in effervescent tablet and/or granule form.
3. The pharmaceutical composition according to claim 1, wherein cefixime can be in the form of its solvates, hydrates, esters, enantiomers, racemates, organic salts, inorganic salts, polymorphs, crystal and amorphous form or in free form and/or a combination thereof.
4. The pharmaceutical composition according to claim 3, wherein cefixime can be in monohydrate, dihydrate, trihydrate and/or anhydrate form.
5. The pharmaceutical composition according to claim 4, wherein cefixime is in trihydrate form.
6. The pharmaceutical composition according to claim 1, wherein clavulanic acid can be in the form of its solvates, hydrates, enantiomers, racemates, organic salts, inorganic salts, polymorphs, crystal and amorphous forms or in free form and/or a combination thereof.
7. The pharmaceutical composition according to claim 6, wherein potassium clavulanate is used.
8. The pharmaceutical composition according to claim 1, wherein said composition comprises pharmaceutically acceptable excipients in addition to potassium clavulanate and cefixime used as the active agents.
9. The pharmaceutical composition according to claim 8, wherein glidants, lubricants, sweeteners, binders, flavoring agents, coloring agents and effervescent couple are used in said composition in addition to potassium clavulanate and cefixime used as the active agents.
10. The pharmaceutical composition according to claim 9, wherein the glidant is selected from a group comprising magnesium silicate, silicon dioxide, starch, talc, tribasic calcium phosphate or a combination thereof.
11. The pharmaceutical composition according to claim 9, wherein the lubricant is selected from a group comprising calcium stearate, magnesium stearate, polyethylene

glycol, PEG 6000, polyvinyl alcohol, potassium benzoate, talc, sodium benzoate or a combination thereof.

12. The pharmaceutical composition according to claim 11, wherein PEG 6000 is used as the lubricant.
13. The pharmaceutical composition according to claim 9, wherein the sweetener can be selected from a group comprising acesulfame, aspartame, fructose, maltitol, maltose, xylitol, saccharine, sodium cyclamate, sucralose, sucrose.
14. The pharmaceutical composition according to claim 13, wherein aspartame is used as the sweetener.
15. The pharmaceutical composition according to claim 9, wherein the effervescent couple can be selected from organic acids such as citric acid, tartaric acid, malic acid, fumaric acid etc. and basic agents such as sodium hydrogen carbonate, sodium carbonate, potassium carbonate and potassium hydrogen carbonate etc.
16. The pharmaceutical composition according to claim 15, wherein citric acid and sodium hydrogen are used as the effervescent couple.
17. The pharmaceutical composition according to claim 15, wherein the ratio of the effervescent acid to the effervescent base is in the rage of 5:1 to 1:1.
18. The pharmaceutical composition according to claim 17, wherein the ratio of the effervescent acid to the effervescent base is in the range of 2:1 to 1.05:1.
19. The pharmaceutical composition according to claim 18, wherein the ratio of the effervescent acid to the effervescent base is in the range of 1.5:1 to 1.1:1.
20. The pharmaceutical composition according to claim 9, wherein the binder is selected from a group comprising ethyl cellulose, gelatin, hypromellose, magnesium aluminum silicate, maltodextrin, polyethylene oxide and povidone.
21. The pharmaceutical composition according to claim 20, wherein povidone is used as the binder.
22. The pharmaceutical composition according to claim 1, wherein the ratio of cefixime to the binder is in the range of 10:1 to 1:1.
23. The pharmaceutical composition according to claim 22, wherein the ratio of cefixime to the binder is in the range of 6:1 to 3:1.
24. The pharmaceutical composition according to claim 1, wherein said composition comprises 20-800 mg cefixime or its pharmaceutically acceptable salts, hydrates, solvates or a combination thereof on an equal amount to it.

25. The pharmaceutical composition according to claim 1, wherein said composition comprises 50-500 mg clavulanic acid or its pharmaceutically acceptable salts, hydrates, solvates or a combination thereof in on equal amount to it.
26. The pharmaceutical composition according to claim 1, wherein clavulanic acid or its derivatives are used with a humectant in the ratio of 1:1.
27. The pharmaceutical composition according to claim 26, wherein the humectant is selected from a group comprising silica; colloidal silica, for instance colloidal silica anhydrous, for example Aerosil® 200, magnesium trisilicate, cellulose powder, Cabosil®, magnesium oxide, calcium silicate, Syloid®, starch, microcrystalline cellulose, talc.
28. The pharmaceutical composition according to claim 27, wherein microcrystalline cellulose or syloid is used as the humectant.
29. The pharmaceutical composition according to claim 28, wherein syloid is used as the humectant.
30. The pharmaceutical composition according to claim 1, wherein 5-50% clavulanic acid or its pharmaceutically acceptable salts, hydrates, solvates or a combination thereof is used in on equal amount to it
31. The pharmaceutical composition according to claim 1, wherein said composition comprises 5-20 % cefixime; 5-50% potassium clavulanate; 0-5% glidant; 0.1-5% lubricant; 0-5% binder; 20-90% effervescent couple; 0,1-10% sweetener; 0.1-5% flavoring agent; 0.1-5% coloring agent with respect to the total weight of the unit dose.
32. The process for the preparation of the pharmaceutical composition described in claim 1, wherein said process comprises the granulation of the active agents cefixime and clavulanic acid or its derivatives, or mixing cefixime, clavulanic acid derivatives and the other excipients through dry blending method and powderizing the mixture, or a combination thereof.
33. The process according to claim 32, wherein clavulanic acid and/or its derivatives are formulated without contacting with water.
34. The process according to claim 32, wherein said process comprises the steps of granulating the binder, the effervescent couple and the sweetener with an aqueous solution; drying the granules; mixing the obtained granules with clavulanic acid and/or its derivative, the coloring agent, the flavoring agent and the lubricant through dry blending; and optionally compressing the mixture in tablet compressing machine.

35. The pharmaceutical composition according to claim 1, wherein said composition is used in the production of a medicament so as to be used in the treatment of gram positive and gram negative bacteria.

INTERNATIONAL SEARCH REPORT

International application No
PCT/TR2011/000119

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K31/545
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)
A61K

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, EMBASE, MEDLINE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2011/093822 A1 (BILGIC MAHMUT [TR]) 4 August 2011 (2011-08-04) the whole document	1-35
Y	CN 100 417 383 C (CHINA PHARMACEUTICAL UNIV [CN]) 10 September 2008 (2008-09-10) the whole document	1-35
Y	WO 2007/086012 A1 (SRINIVAS JEGANNATHAN [IN]) 2 August 2007 (2007-08-02) the whole document	1-35

-/--

[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
20 October 2011	04/11/2011

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	Sindel, Ulrike

1

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/TR2011/000119

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	RAWAT DEEPTI ET AL: "IN VITRO EVALUATION OF A NEW CEFIXIME-CLAVULANIC ACID COMBINATION FOR GRAM-NEGATIVE BACTERIA", SOUTHEAST ASIAN JOURNAL OF TROPICAL MEDICINE AND PUBLIC HEALTH, PROJECT OD SEAMEO, BANGKOK, vol. 40, no. 1, 1 January 2009 (2009-01-01), pages 131-139, XP002633201, ISSN: 0125-1562 the whole document -----	1-35

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/TR2011/000119

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011093822 A1	04-08-2011	WO 2011093822 A1	04-08-2011
		WO 2011093829 A1	04-08-2011
CN 100417383 C	10-09-2008	NONE	
WO 2007086012 A1	02-08-2007	NONE	