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(54) Title: PARENTERAL COMPOSITION COMPRISING A FLUOROQUINOLONE COMPOUND AND A NITROIMIDAZOLE COMPOUND

(57) Abstract: The present invention relates to novel parenteral compositions comprising at least one fluoroquinolone compound and at least one nitroimidazole compound. It further relates to processes for preparing such compositions. It also relates to method of treating acute condition of mixed infections using compositions of the present invention.

PARENTERAL COMPOSITION COMPRISING A FLUOROQUINOLONE COMPOUND AND A NITROIMIDAZOLE COMPOUND

Field of the Invention

The present invention relates to a novel parenteral composition comprising at least one fluoroquinolone compound and at least one nitroimidazole compound.

Background of the Invention

Anaerobes are an important component of many serious infections, especially complicated intra-abdominal (IAI) and acute pelvic (PI) infections in addition to aerobes. Treatment regimen should adequately cover anaerobic, microaerophillic and aerobic organisms in such mixed infections. Appropriate management of mixed aerobic and anaerobic infections requires administration of antimicrobials that are effective against both aerobic and anaerobic components of the infection in addition to surgical intervention where indicated. Regimens can be selected on the basis of the usual bacteriology and how that bacteriology may have been modified by specific circumstances (e.g., hospitalization, antimicrobial therapy, resistance patterns). There are usually several options available. Drugs providing coverage against anaerobes include penicillin G, chloramphenicol, imipenem, ampicillin-sulbactam, clindamycin, cefoxitin, piperacillin, cefotaxime, ceftizoxime, cefoperazone, moxalactam, cefotetan, cefipime or a combination of antibiotics.

The fluoroquinolones exhibit concentration-dependent bactericidal activity by inhibiting the activity of DNA gyrase and topoisomerase, enzymes essential for bacterial DNA replication. The fluoroquinolones are active against *Neisseria , Haemophilus influenzae , Moraxella catarrhalis , Mycoplasma , Chlamydia* and *Chlamydophila , Legionella ,* Enterobacteriaceae, *Pseudomonas aeruginosa.* The fluoroquinolones are also active against *Mycobacterium tuberculosis*, some atypical mycobacteria, and methicillin-sensitive staphylococci, but nosocomial methicillin-resistant staphylococci are usually resistant. The older fluoroquinolones have poor activity against streptococci and anaerobes. Newer fluoroquinolones have reliable activity against streptococci (including *Streptococcus pneumoniae* with reduced penicillinsensitivity) and some anaerobes. As use has increased, resistance is developing among Enterobacteriaceae, *P. aeruginosa*, *S. pneumoniae,* and *Neisseria,* particularly among older fluoroquinolones. Ciprofloxacin,

gatifloxacin, levofloxacin, moxifloxacin, ofloxacin, and trovafloxacin can be administered orally and parenterally; gemifloxacin and norfloxacin are available only orally.

The antimicrobial activity of nitroimidazole is due to the reduction of the nitro group to a more reactive amine that attacks microbial DNA, brings about loss of helical structure of DNA and subsequent DNA breakage thus inhibiting further synthesis and causing degradation of existing DNA. Nitroimidazoles derivatives include metronidazole, tinidazole, ornidazole, nimorazole, secnidazole, azanidazole and propenidazole.

Ornidazole is a nitroimidazole derivative active against several protozoa and several strains of anaerobic bacteria. Ornidazole is effective against *Trichomonas vaginalis*, *Entamoeba histolytica* and *Giardia lamblia*. It also covers certain anaerobic bacteria such as Bacteroides, Clostridium spp., Fusobacterium spp., and anaerobic cocci. Ornidazole is indicated for treatment of bacterial vaginosis (non-specific vaginitis), trichomoniasis (genitourinary infections in women and men due to Trichomonas vaginalis), amoebiasis, giardiasis (lambliasis), infections due to anaerobic bacteria, and prophylaxis during surgical interventions, particularly those involving the colon, and in gynecological operations.

Injectables or infusions containing ofloxacin, ofloxacin hydrochloride, ciprofloxacin or ornidazole are available in the market that can be useful in acute conditions.

U.S. Patent No. 4,957,922 relates to infusion solutions of ciprofloxacin which contain 0.015 to 0.5g of the active compound per 100ml of aqueous solution and an amount of physiologically tolerated acid sufficient to dissolve the active compound and to stabilize the solution. The infusion solutions are found to have a low toxicity and a broad spectrum of antibacterial activity against gram-positive and gram-negative microbes, in particular against Enterobacteriaceae; especially including those which are resistant to various antibiotics such as, for example, penicillins, cephalosporins, aminoglycosides, sulphonamides and tetracyclines.

U.S. Patent Nos. 4,705,789 and 4,808,583 relate to storage stable solutions containing piperazinyl-quinolone- or piperazinyl-azaquinolone-carboxylic acids (ciprofloxacin) with lactic acid.

U.S. Patent Publication No. 2003/0073646 A1 discloses a composition having synergistic effective amounts of one or more antibacterial agents, a nitroimidazole, and an antifungal agent effective against a Candida species. The compositions are particularly useful in the treatment of genitourinary infections.

U.S. Patent No. 7,304,075 relates to an aqueous solution consisting of sitafloxacin, sodium chloride, and a pH adjusting agent selected from the group consisting of one or both of hydrochloric acid and sodium hydroxide.

Russian Patent No. RU 2245134C1 discloses an antibacterial composition containing ofloxacin for injection, in which trilon-B and sodium chloride were used as additives.

In treating mixed infections, no single antimicrobial agent would be adequate to provide desired coverage for both gram-positive and gram-negative aerobes and anaerobes. A combination of at least two antimicrobials is required. A variety of oral formulations containing combination of fluoroquinolone and nitroimidazole in the form of tablet, suspension and syrup, and are currently commercially available for the treatment of mixed infections. For instance combination of ofloxacin and tinidazole, ofloxacin and metronidazole, ofloxacin and ornidazole, gatifloxacin and ornidazole, norfloxacin and ornidazole, levofloxacin and ornidazole, ciprofloxacin and ornidazole, norfloxacin and metronidazole, ciprofloxacin and tinidazole, norfloxacin and tinidazole, metronidazole and nalidixic acid are available.

However, none of the available oral formulations can be used for treating patients with acute conditions. In treating patients with acute condition of mixed infections, especially like mixed intra-abdominal and pelvic infections or in surgical prophylaxis, parenteral formulations containing combination of fluoroquinolones and nitroimidazoles are needed to provide faster onset of action.

It is also known that aqueous formulations containing fluoroquinolones lack stability to light. Specifically, in aqueous solution fluoroquinolones undergo decomposition on being irradiated with light, resulting in reductions of active content, change in pH and generating related substances.

It is therefore desirable to have a stable formulation containing combination of fluoroquinolones and nitroimidazoles with faster onset of action, for treating patients in acute mixed infection conditions. Further it advantageous to have a synergistic

combination therapy to reduce the dosage required for a given therapeutic effect compared to those required using treatment with fluoroquinolone or a nitroimidazole alone, thereby minimizing possibly undesirable side effects.

Summary of the Invention

In one aspect, the present invention relates to an aqueous parenteral composition comprising:

(a) at least one fluoroquinolone compound;

(b) at least one nitroimidazole compound, and

(c) one or more pharmaceutically acceptable excipients.

Embodiments of the composition may include one or more of the following features. For example, the pH of the composition may be in the range of 3 to 6.

In one embodiment, fluoroquinolone compound of the composition may include, but are not limited to, compounds such as alatrofloxacin, balofloxacin, ciprofloxacin, clinafloxacin, danofloxacin, difloxacin, enoxacin, enrofloxacin, garenoxacin, gatifloxacin, gemifloxacin, grepafloxacin, levofloxacin, lomefloxacin, marbofloxacin, moxifloxacin, nadifloxacin, norfloxacin, ofloxacin, orbifloxacin, pefloxacin, sitafloxacin, sparfloxacin, tosufloxacin and trovafloxacin. More preferably the fluoroquinolone is ofloxacin.

In another embodiment, nitroimidazole compound of the composition may include, but are not limited to, compounds such as metronidazole, tinidazole, ornidazole, nimorazole, secnidazole, azanidazole and propenidazole. More preferably the nitroimidazole is ornidazole.

It is another aspect to provide a process for preparing an aqueous parenteral composition comprising the steps of:

(a) preparing an aqueous solution having dissolved therein

– at least one fluoroquinolone compound,

– at least one nitroimidazole compound,

– one or more pharmaceutically acceptable excipients; and

(b) adjusting the pH of the aqueous solution between 3 to 6.

The pharmaceutically acceptable excipients may be one or more of other formulating agents such as complexing agents, antioxidants, tonicity agents and/or agents to adjust the pH.

It is yet another aspect to provide a method for treating acute condition of mixed infections, especially like mixed intra-abdominal and pelvic infections or in surgical prophylaxis, by administering an aqueous parenteral composition comprising:

(a) at least one fluoroquinolone compound;

(b) at least one nitroimidazole compound, and

(c) one or more pharmaceutically acceptable excipients

wherein the pH of the aqueous composition between 3 to 6.

The method may further include administering other antibacterial or pharmaceutical agents.

The details of one or more embodiments of the inventions are set forth in the description below. Other features and objects of the invention will be apparent from the description and examples.

Detailed Description of the Invention

In treating acute condition of mixed infections, agents having broad coverage for both gram-positive and gram-negative aerobes and anaerobes are usually desired. Dosage form containing combination of fluoroquinolones and nitroimidazoles with faster onset of action would be preferred over single agents in such acute conditions. The half-lives of some fluoroquinolones and nitroimidazoles fall in the same range and hence, the time course of action of the two drugs would be similar, which is an important criterion for the selecting two different drugs for treating acute conditions. Further studies show when fluoroquinolones and nitroimidazoles taken together show synergistic effect against some species of anaerobic bacteria such as *B. fragilis*.

The inventors have developed a stable aqueous parenteral composition comprising:

(a) at least one fluoroquinolone compound;

(b) at least one nitroimidazole compound and

(c) one or more pharmaceutically acceptable excipients

wherein the pH of the aqueous composition between 3 to 6.

The aqueous parenteral composition (herein referred as "composition") of the present invention with the pH range of 3 to 6 found to be stable against light and does not led to change in active content or pH or generating related substances, during storage.

The concentration of fluoroquinolone compound and nitroimidazole compound (herein referred as "actives") in the aqueous solution is not particularly limited and can be

selected according to the purpose of use and method of use within a range of solubility of actives in water (or water at a particular pH). A suitable concentration of actives may range from 0.01 to 20 mg/ml.

The composition of the present invention may be of infusion, in the form of dosage units suitable with extractable contents of from, 10 to 1000ml, preferably 50 to 500ml. The dosage units may be dispensed in a single-dose or multiple-dose containers.

The composition of the present invention may be isotonic with the tissue fluid of the human or is slightly hypo or hypertonic. The osmolality of the composition may be 0.20 to 0.70 Osm/kg, preferably 0.26 to 0.39 Osm/kg and is adjusted by isotonicizing agents such as, but limited not to, sodium chloride, sorbitol, mannitol, glucose, D-glucose, sucrose, xylitol, fructose and glycerol or mixtures of such substances. It is also possible where appropriate to employ for this purpose substances which are present in conventional, commercially available infusion vehicle solutions. Customary infusion vehicle solutions include infusions with addition of electrolytes without carbohydrates, such as sodium chloride solution, potassium chloride solution, Ringer's lactate solution and others, and those with carbohydrates, and solutions to supply amino acids, in each case with or without carbohydrate content.

The composition of the present invention may also be prepared as lyophilizates which can be prepared by customary techniques and which are converted into the infusion solutions by dissolution in solvents suitable for this purpose such as, for example, conventional infusion vehicle solutions. Lyophilizates of this type can be obtained by freeze-drying of various starting solutions such as, for example, the infusion solutions according to the invention. It is likewise possible to freeze-dry considerably more dilute solutions as well as considerably more concentrated solutions than the infusion solutions according to the invention.

The composition of the present invention may also contain other pharmaceutically acceptable excipients in the capacity of thickeners, resorbents, light-protection agents, absorption inhibitors, crystallization accelerators, absorption accelerators, crystallization retardants, complexing agents, antioxidants, isotonicizing agents and/or agents to adjust the pH.

Suitable examples of pH adjusting agents include, but are not limited to, hydrochloric acid, sulfuric acid, and phosphoric acid; inorganic acid salts such as sodium

hydrogencarbonate, sodium carbonate, sodium hydrogenphosphate, sodium dihydrogenphosphate, trisodium phosphate, dipotassium phosphate, potassium dihydrogenphosphate, sodium sulfite, sodium hydrogensulfite, and sodium thiosulfate; organic acids such as acetic acid, lactic acid, succinic acid, maleic acid, tartaric acid, citric acid, ascorbic acid, salicylic acid, benzoic acid, methanesulfonic acid, and thioglycolic acid; organic acid esters such as ethyl lactate; organic acid salts such as sodium citrate, disodium citrate, sodium gluconate, calcium citrate, sodium lactate, sodium acetate, sodium pyrophosphate, sodium benzoate, sodium caprylate, and sodium thioglycolate; inorganic salts such as sodium hydroxide; and organic amine compounds such as monoethanolamine, diethanolamine, triethanolamine, ethylenediamine, meglumine, and trometamol.

In order to maintain the pH, suitable buffer system may be used. Examples of buffer system may include, but are not limited to, phosphoric acid; glycine; sodium citrate; histidine; citric acid; acetic acid; tromethamine; ammonium sulfate; and combinations thereof. The aforementioned components are understood to include the salts, hydrates and solvates thereof. Thus, for example, phosphoric acid includes the sodium phosphate or potassium phosphate salts, among other salts. Preferred buffer systems include sodium phosphate monobasic, sodium phosphate dibasic, or a combination thereof. More preferred buffer systems include sodium phosphate monobasic monohydrate, sodium phosphate dibasic anhydrous, or a combination thereof. As used herein, the phrase "organic buffer" refers to a buffer comprising at least one organic compound. Non-limiting examples of suitable organic buffers include: glycine; sodium citrate; histidine; citric acid; acetic acid; and combinations thereof.

Suitable examples of antioxidants may include, but are not limited to, propyl gallate, butylated hydroxytoluene, and alpha-D-tocopherol.

The composition can be sterilized by usual manner, for example, filtration or heating. Sterilization may be preceded or followed by packing into containers. If desired, the composition of the present invention can contain pharmaceutically acceptable additives, such as dissolving aids, buffering components, stabilizers, and the like.

The composition can be dispensed into suitable container for a single dose or for multiple dose. Without intending to effect a restriction hereby, in general glass bottles or bags made of plastic sheets which are suitable for medical use are employed for this

purpose. Polyolefin-based PVC-free bags are particularly preferred. To improve storability, these bags can, where appropriate, be provided with a further outer packaging.

The composition of the present invention may be administered to any part, organ, interstice or cavity of a patient's body that is subject to an infection. For example the composition may be administered by, but not limited to, intravenously, intramuscularly, subcutaneously, ophthalmically, subconjuctivally, intraocularly, via anterior eye chamber injection, intravitreally, intraperitoneally, intrathecally, intracystically, intrapleurally, intranasally, topically, via wound irrigation, intradermally, intrabuccally, intra-abdominally, intra-articularly, intra-aurally, intrabronchially, intracapsularly, intrameningeally, intrapulmonarilly, via inhalation, via endotracheal or endobronchial installation, via direct installation into pulmonary cavities, intraspinally, intrasynovially, intrathoracically, via thoracostomy irrigation, vaginally, epidurally, rectally, intracistemally, intravascularly, intraventricularly, intraosseously, via irrigation of infected bone, and via application as part of any admixture with cement for prosthetic devices.

The present invention is illustrated below by reference to the following examples. However, one skilled in the art will appreciate that the specific methods and results discussed are merely illustrative of the invention, and not to be construed as limiting the invention.

Examples:

Composition

S. No.	Ingredients	Example 1	Example 2
1	Ofloxacin	0.2%	0.2%
2	Ornidazole	0.5%	0.5%
3	Sodium Chloride	0.9%	-
4	Dextrose Monohydrate	-	5.0%
5	1N Sodium Hydroxide Solution	q.s. to pH 3.42	q.s. to pH 3.60
6	5% v/v Hydrochloric Acid Solution	q.s. to pH 3.42	q.s. to pH 3.60
7	Water for Injection	to 100 ml	to 100 ml

Procedure

1. Sodium chloride/Dextrose was dissolved in water for injection and purged with nitrogen gas.
2. To the solution of step 1, ofloxacin and ornidazole were added and stirred.
3. The pH of the above solution is adjusted to desired pH range.
4. The final solution is filtered and filled in USP type I glass vials and terminally autoclaved.

Stability studies:

The compositions prepared in above examples were subjected to various stability studies like, degradation study, photostability study and multiple autoclave study.

Degradation study

The composition of Example 1 and 2 were kept at 60°C for 15 days to check the degradation of actives. The results are summarized in Table 1.

Table 1

Composition	Period	Color	pH	Clarity	% Ofloxacin	% Ornidazole
Example 1	Initial	Yellow	3.42	Clear	100%	100%
	After 15 days	Yellow	3.23	Clear	103%	99.76%
Example 2	Initial	Yellow	3.60	Clear	100%	100%
	After 15 days	Yellow	3.50	Clear	103.9%	101.10%

Photostability study

The composition of Example 1 and 2 were exposed to light providing an overall illumination of not less than 1.2 million lux hours and an integrated near ultraviolet energy of not less than 200 watt hours/square meter in a photo stability chamber. The results are summarized in Table 2.

Table 2

Composition	Condition	Color	pH	Clarity	% Ofloxacin	% Ornidazole
Example 1	Initial	Yellow	3.42	Clear	100%	100%
	After exposure	Yellow	3.34	Clear	97.53%	102.01%
Example 2	Initial	Yellow	3.60	Clear	100%	100%
	After exposure	Yellow	3.29	Clear	91.83%	97.63%

Multiple autoclave study

The composition of Example 1 and 2 were subjected to multiple autoclave study at 121°C for 20 min. The results are summarized in Table 3.

Table 3

Composition	Condition	Color	pH	Clarity	% Ofloxacin	% Ornidazole
Example 1	Initial	Yellow	3.42	Clear	100%	100%
	After autoclave	Yellow	3.48	Clear	105.0%	100.6%
Example 2	Initial	Yellow	3.60	Clear	100%	100%
	After autoclave	Yellow	3.59	Clear	103.0%	100.5%

While several particular forms of the invention have been illustrated and described, it will be apparent that various modifications and combinations of the invention detailed in the text can be made without departing from the spirit and scope of the invention. Accordingly, it is not intended that the invention be limited, except as by the appended claims.

We Claim:

1. An aqueous parenteral composition comprising:
   (a) at least one fluoroquinolone compound,
   (b) at least one nitroimidazole compound and
   (c) one or more pharmaceutically acceptable excipients.

2. The composition according to claim 1, wherein the pH of the composition is in the range of 3 to 6.

3. The composition according to claim 1, wherein the fluoroquinolone compound is selected from alatrofloxacin, balofloxacin, ciprofloxacin, clinafloxacin, danofloxacin, difloxacin, enoxacin, enrofloxacin, garenoxacin, gatifloxacin, gemifloxacin, grepafloxacin, levofloxacin, lomefloxacin, marbofloxacin, moxifloxacin, nadifloxacin, norfloxacin, ofloxacin, orbifloxacin, pefloxacin, sitafloxacin, sparfloxacin, tosufloxacin and tovafloxacin.

4. The composition according to claim 1, wherein the fluoroquinolone compound is ofloxacin.

5. The composition according to claim 1, wherein the nitroimidazole compound is selected from ronidazole, tinidazole, ornidazole, nimorazole, secnidazole, azanidazole and propenidazole.

6. The composition according to claim 1, wherein the nitroimidazole compound is ornidazole.

7. The composition according to claim 1, wherein the actives are present in a concentration of 0.01 to 20mg/ml.

8. The composition according to claim 1, wherein the pharmaceutically acceptable excipients comprises one or more of complexing agents, antioxidants, tonicity agents and/or pH adjusting agents.

9. A process for preparing an aqueous parenteral composition comprising the steps of:
   (a) preparing an aqueous solution having dissolved therein
      – at least one fluoroquinolone compound,
      – at least one nitroimidazole compound,
      – one or more pharmaceutically acceptable excipients; and
   (b) adjusting the pH of the aqueous solution between 3 to 6.

10. A method for treating acute condition of mixed infections, especially like mixed intra-abdominal and pelvic infections or in surgical prophylaxis, by administering an aqueous parenteral composition comprising:

(a) at least one fluoroquinolone compound;

(b) at least one nitroimidazole compound and

(c) one or more pharmaceutically acceptable excipients

wherein the pH of the aqueous composition between 3 to 6.

11. A method according to claim 10, comprising further administration of other antibacterial or pharmaceutical agents.

12. An aqueous parenteral composition comprising at least one fluoroquinolone compound, at least one nitroimidazole compound and one or more pharmaceutically acceptable excipients, substantially as described and illustrated herein.

INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/4164 A61K31/496 A61K45/06 A61K9/00
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, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHAUDHARY, M ET AL.: "Sub-Chronic Toxicity Study of Fixed Dose Combination of Ofloxacin-Ornidazole in Mus Musculus Mice" OPEN TOXICOLOGY JOURNAL 2009 BENTHAM SCIENCE PUBLISHERS B.V. NLD LNKD-DOI:10.2174/1874340400903010024, vol. 3, 19 March 2009 (2009-03-19), pages 24-29, XP002597864 ISSN: 1874-3404 the whole document ----- -/--	1-12

[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

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"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
25 August 2010	13/10/2010

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	Sproll, Susanne

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2010/052037

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1991, GOODWIN S D ET AL: "COMPATIBILITY OF CIPROFLOXACIN INJECTION WITH SELECTED DRUGS AND SOLUTIONS" XP002597865 Database accession no. PREV199192133599 * abstract -----	1-12
X,P	SHRIVASTAVA S M ET AL: "Comparative evaluation of fixed dose combination of ofloxacin and ornidazole against some aerobic bacteria" TRENDS IN MEDICAL RESEARCH 2009 ACADEMIC JOURNALS INC. USA LNKD- DOI:10.3923/TMR.2009.30.34, vol. 4, no. 2, 2009, pages 30-34, XP002597866 USA ISSN: 1819-3587 the whole document -----	1-12
X	MATTHAIOU D K ET AL: "Ciprofloxacin/metronidazole versus beta-lactam-based treatment of intra-abdominal infections: a meta-analysis of comparative trials" INTERNATIONAL JOURNAL OF ANTIMICROBIAL AGENTS, ELSEVIER SCIENCE, AMSTERDAM, NL LNKD- DOI:10.1016/J.IJANTIMICAG.2006.04.005, vol. 28, no. 3, 1 September 2006 (2006-09-01), pages 159-165, XP025082244 ISSN: 0924-8579 [retrieved on 2006-09-01] the whole document -----	1-12
X	BOECKH M ET AL: "PHARMACOKINETICS AND SERUM BACTERICIDAL ACTIVITIES OF QUINOLONES IN COMBINATION WITH CLINDAMYCIN METRONIDAZOLE AND ORNIDAZOLE" ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, vol. 34, no. 12, 1990, pages 2407-2414, XP002597867 ISSN: 0066-4804 the whole document -----	1-12
X	US 2003/073646 A1 (MILANKOVITS MARTON [HU]) 17 April 2003 (2003-04-17) cited in the application paragraphs [0010], [0066], [0070]; claims 1,6; examples 2,13 -----	1-12

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2010/052037

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 1 875 910 A1 (NANJING SANHOME PHARMACEUTICAL [CN]) 9 January 2008 (2008-01-09) examples 7-12	1-12
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