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(71) Applicant *(for all designated States except US)*: **PHARMACIA & UPJOHN COMPANY** [US/US]; 301 Henrietta Street, Kalamazoo, MI 49001 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: **BATTS, Donald, H.** [US/US]; 4303 Old Colony, Kalamazoo, MI 49008 (US).

(74) Agent: **STEIN, Bruce**; Intellectual Property Legal Services, Pharmacia & Upjohn Company, 301 Henrietta Street, Kalamazoo, MI 49001 (US).

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(54) Title: ADMIXTURE OF LINEZOLID AND OTHER ANTIBACTERIAL AGENTS

(57) Abstract: The present invention is an aqueous admixture of linezolid and an antibacterial agent selected from the group consisting of gentamicin, tobramycin, aztreonam, cefazolin, ceftazidime, piperacillin, ciprofloxacin, ofloxacin, levofloxacin for IV administration.

ADMIXTURE OF LINEZOLID AND OTHER ANTIBACTERIAL AGENTS

CROSS-REFERENCE TO RELATED APPLICATIONS

None.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention is a mixture of sterile solutions of linezolid and particular antibacterial agents.

2. Description of the Related Art

US Patent 5,688,792 (EXAMPLE 5) discloses the antibacterial agent, linezolid.

The 53rd edition of the Physicians Desk Reference (PDR), Medical Economics Company, Montvale, NJ, 1999 discloses the other antibacterial agents of the invention. See for gentamicin (p. 964) , tobramycin (599, 1562), aztreonam (p.820), cefazolin (p. 3023), ceftazidime (p.1100), piperacillin (p. 1531), ciprofloxacin (p. 647), ofloxacin (p. 2180), and levofloxacin (2192).

It is known to those skilled in the art that mixing solutions of pharmaceutical agents can result in physical and/or chemical instability rendering the mixture unfit for pharmaceutical use.

US provisional patent application Serial No. 60/191,383 discloses a polyolefin lined container for linezolid IV pharmaceutical formulations.

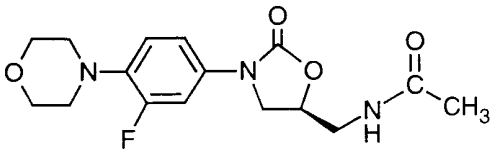
SUMMARY OF INVENTION

Disclosed is an aqueous pharmaceutical composition for IV administration of linezolid and one or more antibacterial agents selected from the group consisting of an aminoglycosides, cephalosporins, aztreonam, quinolones and penicillins and pharmaceutically acceptable salts thereof where such exist.

Also disclosed is a method of treating a human with a bacterial infection which comprises IVadministeration to the infected human an aqueous pharmaceutical composition of linezolid and one or more antibacterial agents selected from the group consisting of an aminoglycosides, cephalosporins, aztreonam, quinolones and penicillins and pharmaceutically acceptable salts thereof where such exist.

DETAILED DESCRIPTION OF THE INVENTION

Linezolid, (S)-N-[[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,



is a known antibacterial agent, see US Patent 5,688,792 (EXAMPLE 5). Linezolid can be used as an oral tablet, capsule or oral suspension or given by IV as a sterile solution.

Gentamicin is a known antibacterial agent, see page 964 of the 53rd Edition of the PDR (1999) and can be given by IV as a sterile solution.

Tobramycin is a known antibacterial agent, see page 599 and 1562 of the 53rd Edition of the PDR (1999) and can be given by IV as a sterile solution.

Aztreonam is a known antibacterial agent, see page 820 of the 53rd Edition of the PDR (1999) and can be given by IV as a sterile solution.

Cefazolin is a known antibacterial agent, see page 3023 of the 53rd Edition of the PDR (1999) and can be given by IV as a sterile solution.

Ceftazidime is a known antibacterial agent, see page 1100 of the 53rd Edition of the PDR (1999) and can be given by IV as a sterile solution.

Piperacillin is a known antibacterial agent, see page 1531 of the 53rd Edition of the PDR (1999) and can be given by IV as a sterile solution.

Ciprofoxacin is a known antibacterial agent, see page 647 of the 53rd Edition of the PDR (1999) and can be given by IV as a sterile solution.

Ofloxacin is a known antibacterial agent, see page 2180 of the 53rd Edition of the PDR (1999) and can be given by IV as a sterile solution.

Levofloxacin is a known antibacterial agent, see page 2192 of the 53rd Edition of the PDR (1999) and can be given by IV as a sterile solution.

Linezolid is a member of a new class of antibacterial agent known as an oxazolidinone and is useful in treating infections caused by gram positive bacteria including gram positive infections that are resistant to other gram positive antibacterial agents.

Often in medical treatment a physician does not know for sure whether or not a bacterial infection is caused by gram positive bacteria or gram negative bacteria or both. Therefore, often a physician desires to use an agent(s) which are effective against both gram positive and gram negative bacteria. Hence, often a physician will

combine two agents, one useful against gram positive bacteria and the other useful against gram negative bacteria. The following agents are known to be useful against gram negative bacteria, gentamicin, tobramycin, aztreonam. The following antibacterial agents are known as 'broad spectrum antibacterials" because they are active against both gram positive and gram negative bacteria, cefazolin, ceftazidime, piperacillin, ciprofloxacin, ofloxacin and levofloxacin.

If one combines sterile solutions of two different agents it is quite possible that there will not be chemical or physical compatibility between the two different sterile solutions and/or agents. In fact, for this very reason, the corporation conducting the clinical trials on linezolid specifically warned physicians against combining the sterile solution of linezolid and other antibacterial agents.

It now has been found that there is both chemical and physical stability between linezolid sterile solution and sterile solutions of the following antibacterial agents; aminoglycosides, cephalosporins, aztreonam, quinolones and penicillins and pharmaceutically acceptable salts thereof where such exist. It is preferred that the antibacterial agent be selected from the group consisting of gentamicin, tobramycin, aztreonam, cefazolin, ceftazidime, piperacillin, ciprofloxacin, ofloxacin and levofloxacin.

When combining an aqueous composition of linezolid with an aqueous composition of the other antibacterial agents the concentration of both linezolid and the other antibacterial agents will be affected by a dilution factor as is well known to those skilled in the art. The actual final concentration of linezolid and/or the other antibacterial agents is not very important. The concentration can vary considerably. What is critical is that the patient receive an antibacterial effective amount of linezolid and an antibacterial effective amount of the other antibacterial agent. The effective amounts for each of these agents, for adults, is as follows: linezolid (about 200 mg to about 600 mg/dose), gentamicin (about 1 mg/kg to about 7.5 mg/kg/dose), tobramycin (about 1 mg/kg to about 7.5 mg/kg/dose), aztreonam (about 500 mg to about 2 g/dose), ciprofloxacin (about 200 mg to about 400 mg/dose), ofloxacin (about 200 mg to about 400 mg/dose), levofloxacin (about 250 mg to about 500 mg/dose), piperacillin sodium (about 2 g to about 4 g/dose), piperacillin/tazobactam (about 2 g to about 4 g/dose based on piperacillin), ceftazidime (about 250 mg to about 2 g/dose) and cefazolin (about 500 mg to about 1 g/dose). One skilled in the art would be able

to calculate an effective amount for children (of various ages and weights) as well as the elderly.

It is preferred that the aqueous pharmaceutical composition of the present invention be an aqueous solution. It is further preferred that the aqueous solution be a sterile solution.

There are different ways that one skilled in the art could make an aqueous pharmaceutical composition of linezolid and an antibacterial agent selected from the group consisting of gentamicin, tobramycin, aztreonam, cefazolin, ceftazidime, piperacillin, ciprofloxacin, ofloxacin and levofloxacin.

First, one can combine an aqueous pharmaceutical composition of linezolid and an aqueous pharmaceutical composition of one of the following agents; gentamicin, tobramycin, aztreonam, cefazolin, ceftazidime, piperacillin, ciprofloxacin, ofloxacin and levofloxacin. If this is done it must be realized that the concentration of each antibacterial agent is being diluted by the other as explained above.

Alternatively, so as not to dilute the linezolid aqueous pharmaceutical composition, it is preferred to add solid antibacterial agent selected from the group consisting of gentamicin, tobramycin, aztreonam, cefazolin, ceftazidime, piperacillin, ciprofloxacin, ofloxacin and levofloxacin to the linezolid aqueous pharmaceutical composition. Also so as not to dilute an aqueous pharmaceutical composition of one of the following antibacterial agents, gentamicin, tobramycin, aztreonam, cefazolin, ceftazidime, piperacillin, ciprofloxacin, ofloxacin and levofloxacin, solid linezolid powder can be added to the aqueous pharmaceutical composition of one of the other antibacterial agents. In addition, should more than one of the non-linezolid antibacterial agents be desired for use with linezolid, it can be added in the same way.

Besides adding solid antibacterial agent to a solution, to keep the dilution factor low, the solid antibacterial agent or linezolid can be suspended or dissolved in an appropriate solvent such as water, ethanol, polyethylene glycol, propylene glycol, DMSO, DMAC, DMI, glycerine and M-pyrol and mixtures thereof. The concentrate can then be added to the aqueous pharmaceutical composition.

The advantage of admixing is to lower the total volume administered and/or to use the same infusion line. The lowering of the total volume to be given to the patient is accomplished in a number of ways by using the admixing of the present invention. For example, an number of antibacterial agents come as concentrates to be diluted

with acceptable diluents. With these concentrates the diluent used is the linezolid sterile solution there by saving the volume of diluent normally used to dilute the other antibacterial agent. Alternatively, other antibacterial agents are marketed as sterile powders which are then compounded into concentrates for dilution. With these sterile powders the first step is performed in making the concentrate. But rather then using a diluent that has no active ingredient, the concentrate is added to linezolid sterile solution (as described above). This reduces the overall volume of aqueous composition administered to the patient. In situations where the antibacterial agent is marketed as a ready to use large volume parenteral sterile solution, there is no way to reduce the volume unless it is combined with linezolid in a concentrated form. If it is combined with sterile aqueous linezolid solution the advantage is that the same infusion line can be used for administering both the linezolid and the other antibacterial agent.

US Patent 5,688,792 discloses that oxazolidinones can be administered IV. The preferred formulation for linezolid IV solution is:

Linezolid	2.0 mg/mL
Sodium Citrate Dihydrate (USP)	1.64 mg/mL
Citric Acid Anhydrous (USP)	0.85 mg/mL
Dextrose Monohydrate (USP)	50.24 mg/mL
Hydrochloric Acid (10%) q.s. to pH 4.8 (pH 4.6 to 5.0)	
Sodium hydroxide (10%) q.s. to pH 4.8 (pH 4.6 to 5.0)	
Water for Injection (USP)	q.s.ad 1.0 mL

The linezolid IV solution is formulated by heating water for injection to 60°. Next the sodium citrate, citric acid and dextrose are added and stirred until dissolved. An aqueous slurry of linezolid is added to the previous mixture and stirred until dissolved. The mixture is cooled to 25° with stirring. The pH is measured and adjusted if necessary. Last the mixture is brought to volume, if necessary, with water for injection. The mixture is filtered, filled into infusion containers, over wrapped and terminally moist heat sterilized.

The aqueous solution for IV administration can be placed in the container which is selected from the group consisting of a bag, a bottle, a vial, a large volume parenteral, a small volume parenteral, a prefilled syringe and a cassette. It is realized that a vial is a bottle. However, those skilled in the art use the term "bottle" to refers

to larger bottles and "vials" to refer to smaller bottles. It is preferred that the container be a bag, a bottle, a vial or a prefilled syringe. It is more preferred that the container be a bag or bottle. It is most preferred that the container be a bag. The shape and/or size of the container is unimportant. It is preferred that the container be a bag sufficient to hold 25 to 2,000 mL of IV solution. It is preferred that the linezolid mixture be put in bags in amounts of 100, 200 or 300 mL of solution however smaller or larger volumes are acceptable.

It is well known to those skilled in the art that pharmaceutical agents administered IV must be sterile. While there are a number of methods to sterilize an IV solution, it is preferred to terminally moist heat or steam sterilize IV solutions of oxazolidinones including those of linezolid. When the term terminally "moist heat sterilize" is used, it refers to and includes steam sterilization.

When terminally moist heat sterilizing an IV solution, the solution is placed in the container in which (1) it will be stored and then transferred to the container from which it will ultimately be administered, or (2) stored and then ultimately administered from the same container to deliver the IV solution to the patient. Therefore, it is imperative that the pharmaceutically active ingredient (oxazolidinone, linezolid) not react with the container in which it is to be terminally moist heat sterilized and stored/stored-administered.

It has been found that when the container-solution contact surface is made of at least 50% polyolefin there is significantly much less loss of linezolid during and following terminal moist heat sterilization. What is essential is that the container-solution contact surface material be primarily a polyolefin; the remainder of the container can be made from polyolefin or other materials. It is preferred that the container-solution contact surface is made of from about 50 to about 100% polyolefin. It is more preferred that the container-solution contact surface is made of from about 70 to about 90% polyolefin. It is more preferred that the container-solution contact surface is made of from about 80% polyolefin. It is even more preferred that the container-solution contact surface is made of polyolefin.

Polyolefins include, for example, polyethylene, polypropylene, polybutenes, polyisoprenes and polypentenes and copolymers and mixtures thereof. It is preferred that the polyolefin be selected from the group consisting of polyethylene and

polypropylene. It is more preferred that the polyolefin be polypropylene or mixture of polypropylene and polyethylene.

The exact dosage and frequency of administration of the aqueous pharmaceutical composition depends on the particular combination of linezolid and antibacterial agent used, the particular condition being treated, the severity of the condition being treated, the age, weight, general physical condition of the particular patient, other medication the individual may be taking as is well known to those skilled in the art and can be more accurately determined by measuring the blood level or concentration of the antibacterial agents in the patient's blood and/or the patient's response to the particular condition being treated.

DEFINITIONS AND CONVENTIONS

The definitions and explanations below are for the terms as used throughout this entire document including both the specification and the claims.

DEFINITIONS

All temperatures are in degrees Centigrade.

Linezolid refers to (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide and pharmaceutically acceptable salts thereof.

Physiological saline refers to an aqueous 0.9% sodium chloride solution.

Pharmaceutically acceptable refers to those properties and/or substances which are acceptable to the patient from a pharmacological/toxicological point of view and to the manufacturing pharmaceutical chemist from a physical/chemical point of view regarding composition, formulation, stability, patient acceptance and bioavailability.

When solvent pairs are used, the ratios of solvents used are volume/volume (v/v).

When the solubility of a solid in a solvent is used the ratio of the solid to the solvent is weight/volume (wt/v).

qsad refers to addition of a sufficient quantity of that material to bring the final composition to the specified volume.

DMSO refers to dimethylsulfoxide [CH_3-SO-CH_3].

DMAC refers to dimethylacetamide [CH_3-CO-N(CH_3)$_2$].

DMI refers to dimethyl isosorbide.

M-PYROL refers to N-methyl-2-pyrrolidone.

EXAMPLES

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, practice the present invention to its fullest extent. The following detailed examples describe how to prepare the various compounds and/or perform the various processes of the invention and are to be construed as merely illustrative, and not limitations of the preceding disclosure in any way whatsoever. Those skilled in the art will promptly recognize appropriate variations from the procedures both as to reactants and as to reaction conditions and techniques.

PREPARATION 1 Linezolid sterile solution:

Linezolid	2.0 mg/mL
Sodium Citrate Dihydrate (USP)	1.64 mg/mL
Citric Acid Anhydrous (USP)	0.85 mg/mL
Dextrose Monohydrate (USP)	50.24 mg/mL
Hydrochloric Acid (10%) q.s. to pH 4.8 (pH 4.6 to 5.0)	
Sodium hydroxide (10%) q.s. to pH 4.8 (pH 4.6 to 5.0)	
Water for Injection (USP)	q.s.ad 1.0 mL

EXAMPLE 1 Linezolid and Gentamicin Sulfate

Linezolid sterile solution (PREPARATION 1) is admixed with commercial gentamicin concentrate. One admixture is stored at 4° and another at 23°. The admixtures were sampled at one, three, five days and seven days. The samples were tested for both chemical and physical stability. The results of the samples for both temperatures show there is good chemical and physical stability over 7 days at 4° and 5 days at 23°. It is concluded that the admixture of linezolid and commercial gentamicin concentrate is acceptable for human use.

EXAMPLE 2 Linezolid and Tobramycin Sulfate

Following the general procedure of EXAMPLE 1 and making non-critical variations, Linezolid sterile solution (PREPARATION 1) is admixed with commercial tobramycin concentrate. The results of the samples for both temperatures show there is good chemical and physical stability over 7 days at 4° and 1 day at 23°. It is concluded that the admixture of linezolid and commercial tobramycin concentrate is acceptable for human use.

EXAMPLE 3 Linezolid and Aztreonam

Following the general procedure of EXAMPLE 1 and making non-critical variations, Linezolid sterile solution (PREPARATION 1) is admixed with

commercial reconstituted aztreonam. The results of the samples for both temperatures show there is good chemical and physical stability over 7 days at 4° and 7 days at 23°. It is concluded that the admixture of linezolid and commercial reconstituted aztreonam is acceptable for human use.

EXAMPLE 4 Linezolid and Cefazolin Sodium

Following the general procedure of EXAMPLE 1 and making non-critical variations, Linezolid sterile solution (PREPARATION 1) is admixed with commercial reconstituted cefazolin. The results of the samples for both temperatures show there is good chemical and physical stability over 7 days at 4° and 3 day at 23°. It is concluded that the admixture of linezolid and commercial cefazolin concentrate is acceptable for human use.

EXAMPLE 5 Linezolid and Ceftazidime

Following the general procedure of EXAMPLE 1 and making non-critical variations, Linezolid sterile solution (PREPARATION 1) is admixed with commercial reconstituted ceftazidime. The results of the samples for both temperatures show there is good chemical and physical stability over 7 days at 4° and 1 day at 23°. It is concluded that the admixture of linezolid and commercial ceftazidime concentrate is acceptable for human use.

EXAMPLE 6 Linezolid and Piperacillin Sodium

Following the general procedure of EXAMPLE 1 and making non-critical variations, Linezolid sterile solution (PREPARATION 1) is admixed with commercial reconstituted piperacillin. The results of the samples for both temperatures show there is good chemical and physical stability over 7 days at 4° and 3 days at 23°. It is concluded that the admixture of linezolid and commercial piperacillin concentrate is acceptable for human use.

EXAMPLE 7 Linezolid and Ciprofloxacin

Following the general procedure of EXAMPLE 1 and making non-critical variations, Linezolid sterile solution (PREPARATION 1) is admixed with commercial ciprofloxacin concentrate. The results of the samples show there is good chemical and physical stability over 7 days at 23°. It is concluded that the admixture of linezolid and commercial ciprofloxacin concentrate is acceptable for human use.

EXAMPLE 8 Linezolid and Ofloxacin

Following the general procedure of EXAMPLE 1 and making non-critical variations, Linezolid sterile solution (PREPARATION 1) is admixed with commercial ofloxacin concentrate. The results of the samples for both temperatures show there is good chemical and physical stability over 7 days at 4° and 7 days at 23°. It is concluded that the admixture of linezolid and commercial ofloxacin concentrate is acceptable for human use.

EXAMPLE 9 Linezolid and Levofloxacin

Following the general procedure of EXAMPLE 1 and making non-critical variations, Linezolid sterile solution (PREPARATION 1) is admixed with commercial levofloxacin concentrate. The results of the samples for both temperatures show there is good chemical and physical stability over 7 days at 4° and 7 days at 23°. It is concluded that the admixture of linezolid and commercial levofloxacin concentrate is acceptable for human use.

CLAIMS

1. An aqueous pharmaceutical composition for IV administration of linezolid and one or more antibacterial agents selected from the group consisting of an aminoglycosides, cephalosporins, aztreonam, quinolones and penicillins and pharmaceutically acceptable salts thereof where such exist.

2. An aqueous pharmaceutical composition according to claim 1 where the antibacterial agent is selected from the group consisting of gentamicin, tobramycin, aztreonam, cefazolin, ceftazidime, piperacillin, ciprofloxacin, ofloxacin, levofloxacin.

3. An aqueous pharmaceutical composition according to claim 1 where the antibacterial agent is gentamicin.

4. An aqueous pharmaceutical composition according to claim 1 where the antibacterial agent is tobramycin.

5. An aqueous pharmaceutical composition according to claim 1 where the antibacterial agent is aztreonam.

6. An aqueous pharmaceutical composition according to claim 1 where the antibacterial agent is cefazolin.

7. An aqueous pharmaceutical composition according to claim 1 where the antibacterial agent is ceftazidime.

8. An aqueous pharmaceutical composition according to claim 1 where the antibacterial agent is piperacillin.

9. An aqueous pharmaceutical composition according to claim 1 where the antibacterial agent is ciprofloxacin.

10. An aqueous pharmaceutical composition according to claim 1 where the antibacterial agent is ofloxacin.

11. An aqueous pharmaceutical composition according to claim 1 where the antibacterial agent is levofloxacin.

12. An aqueous pharmaceutical composition according to claim 1 where the aqueous composition is a solution.

13. An aqueous pharmaceutical composition according to claim 12 where the solution is sterile.

14. An aqueous pharmaceutical composition according to claim 1 where the linezolid-antibacterial agent mixture is made by combining an aqueous solution of linezolid and an aqueous solution of the antibacterial agent.

15. An aqueous pharmaceutical composition according to claim 1 where the linezolid-antibacterial agent mixture is made by combining an aqueous solution of linezolid and solid antibacterial agent.

16. An aqueous pharmaceutical composition according to claim 1 where the linezolid-antibacterial agent mixture is made by combining an aqueous solution of the antibacterial agent and solid linezolid.

17. An aqueous pharmaceutical composition according to claim 1 where the linezolid-antibacterial agent mixture is made by combining an aqueous solution of linezolid and a concentrate of the antibacterial agent.

18. An aqueous pharmaceutical composition according to claim 1 where the linezolid-antibacterial agent mixture is made by combining an aqueous solution of the antibacterial agent and a concentrate of linezolid.

19. An aqueous pharmaceutical composition according to claim 1 where the IV pharmaceutical composition is in a container where the container-solution contact surface material made of at least 50% polyolefin.

20. An aqueous pharmaceutical composition according to claim 19 where the container is selected from the group consisting of a bag, a bottle, a vial, a large volume parenteral, a small volume parenteral, a prefilled syringe and a cassette.

21. An aqueous pharmaceutical composition according to claim 20 where the container is a bag, a bottle, a vial and a prefilled syringe.

22. An aqueous pharmaceutical composition according to claim 19 where the container-solution contact surface is made of polyolefin or made primarily of polyolefin.

23. An aqueous pharmaceutical composition according to claim 22 where the container-solution contact surface is made of from about 50 to about 100% polyolefin.

24. An aqueous pharmaceutical composition according to claim 23 where the container-solution contact surface is made of from about 70 to about 90% polyolefin.

25. An aqueous pharmaceutical composition according to claim 22 where the container-solution contact surface is made of polyolefin.

26. An aqueous pharmaceutical composition according to claim 22 where the polyolefin is selected from the group consisting of polyethylene, polypropylene, polybutenes, polyisoprenes and polypentenes and copolymers and mixtures thereof.

27. A method of treating a human with a bacterial infection which comprises IV administration to the infected human an aqueous pharmaceutical composition of linezolid and one or more antibacterial agents selected from the group consisting of an aminoglycosides, cephalosporins, aztreonam, quinolones and penicillins and pharmaceutically acceptable salts thereof where such exist.

28. A method of treating a human with a bacterial infection according to claim 27 where the antibacterial agent is selected from the group consisting of gentamicin,

tobramycin, aztreonam, cefazolin, ceftazidime, piperacillin, ciprofloxacin, ofloxacin, levofloxacin.

29. A method of treating a human with a bacterial infection according to claim 17 where the aqueous composition is a solution.

30. A method of treating a human with a bacterial infection according to claim 29 where the solution is sterile.

31. A method of treating a human with a bacterial infection according to claim 27 where IV pharmaceutical composition is in a container where the container-solution contact surface material made of at least 50% polyolefin.

32. A method of treating a human with a bacterial infection according to claim 31 where the container-solution contact surface is made of polyolefin or made primarily of polyolefin.

33. A method of treating a human with a bacterial infection according to claim 32 where the container-solution contact surface is made of polyolefin.

34. A method of treating a human with a bacterial infection according to claim 33 where the polyolefin is selected from the group consisting of polyethylene, polypropylene, polybutenes, polyisoprenes and polypentenes and copolymers and mixtures thereof.