Title: AQUEOUS CONCENTRATED FORMULATION OF LINEZOLID

Abstract: The invention provides aqueous concentrated formulation of linezolid. More particularly, the invention provides aqueous concentrated formulation of linezolid comprising at least one solubilizer wherein the formulation is preferably administered intravenously.
AQUEOUS CONCENTRATED FORMULATION OF LINEZOLID

FIELD OF INVENTION
The invention provides aqueous concentrated formulation of linezolid and method of preparing and using the same.

More particularly, the invention provides aqueous concentrated formulation of linezolid comprising at least one solubilizer wherein the formulation is preferably administered intravenously.

BACKGROUND OF THE INVENTION AND RELATED PRIOR ARTS
Parenteral routes of administration, including subcutaneous, intramuscular and intravenous injection, offer numerous benefits over oral delivery in particular situations, for a wide variety of drugs. For example, parenteral administration of a drug typically results in attainment of a therapeutically effective blood serum concentration of the drug in a shorter time than is achievable by oral administration. This is especially true of intravenous injection, whereby the drug is placed directly in the bloodstream. Parenteral administration also results in more predictable blood serum concentrations of the drug, because losses in the gastrointestinal tract due to metabolism, binding to food and other causes are eliminated. For similar reasons, parenteral administration often permits dose reduction. Parenteral administration is generally the preferred method of drug delivery in emergency situations, and is also useful in treating subjects who are uncooperative, unconscious, or otherwise unable or unwilling to accept oral medication.

One particular form of parenteral administration is intravenous administration, in which the active ingredient is administered by means of an injection or infusion into a vein of the patient. While in the case of intravenous injection, the entire quantity of active ingredient is available in the body immediately after
administration; intravenous infusion makes it possible to administer the entire quantity of active ingredient over a longer period of time.

Pharmaceutical active ingredients are administered intravenously virtually exclusively by means of an aqueous solution of a particular active ingredient, as miscibility of the administered solution with the patient’s blood is an essential prerequisite for safe administration. If this miscibility is not present, the patient runs the risk of life-threatening embolisms or severe necrosis. While intravenously administrable oil-in-water emulsions comprising a lipophilic active ingredient in the disperse phase are known, the capacity of such emulsions to absorb the lipophilic active ingredient is restricted, on the one hand, by the solubility of the active ingredient in the oil phase and, on the other, by the physical stability of the emulsion, such that this mode of administration has not become widespread.

Intravenous administration of active ingredients is thus conventionally limited to those active ingredients which are characterized by sufficient water solubility. This ensures that a quantity of the active ingredient which is necessary for satisfactory treatment of the patient may be completely dissolved in the aqueous medium to be administered. Numerous active ingredients with poor to very poor water solubility, on the other hand, may conventionally only be administered to the patient by other routes, for example orally or rectally, as the volume of the aqueous medium which would be required completely to dissolve the active ingredient is such that intravenous administration is no longer possible.

Oxazolidinones are a class of antibacterial agents with a unique mechanism of inhibiting bacterial protein synthesis by inhibiting the formation of ribosomal initiation complex involving 30S and 50S ribosomes. Due to their unique mechanism of action, these compounds are active against pathogens resistant to other clinically useful antibiotics.
Preferred oxazolidinones are compounds selected from linezolid, N-((5S)-3-(3-fluoro-4-(2-fluoroethyl)-3-oxopiperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide, (S)-N-[[3-[5-(3-pyridyl)thiophen-2-yl]-2-oxo-5-oxazolidinyl]methyl]acetamide, (S)-N-[[3-[5-(4-pyridyl)pyrid-2-yl]-2-oxo-5-oxazolidinyl]methyl]acetamide hydrochloride and N-[[5(S)-3-[4-(1,1-dioxido-4-thiomorpholinyl)-3,5-difluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. In a preferred embodiment, the oxazolidinone is linezolid.

The invention is illustrated herein with particular reference to linezolid, and it will be understood that any other oxazolidinone antimicrobial drug can, if desired, be substituted in whole or in part for linezolid, with appropriate adjustment in concentration and dosage ranges, in the compositions and methods herein described.

Linezolid, chemically known as (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl) phenyl]-2-oxo-5-oxazolidinyl] methyl]acetamide is an antimicrobial agent of oxazolidinone class (U.S. Pat. No. 5,688,792), having the empirical formula C16H20FN3O4 and the following structure:

\[
\text{\includegraphics{linezolid_structure.png}}
\]

Linezolid exhibits strong antibacterial activity against gram-positive organisms including those of the following genera: Staphylococcus (e.g., Staphylococcus aureus, Staphylococcus epidermis), Streptococcus (e.g., Streptococcus viridans, Streptococcus pneumoniae), Enterococcus (e.g., Enterococcus fecalis, Enterococcus faecium), Bacillus Corynebacterium, Chlamydia and Neisseria. Many such gram-positive organisms have developed significant levels of resistance to other antibiotics.
Many oxazolidinone compounds have relatively low solubility in water; in the case of linezolid, for example, the solubility at ambient temperature is less than 3 mg/ml.

Linezolid is currently marketed by Pfizer under the trade names Zyvox® (in the United States, United Kingdom, Australia, and several other countries), Zyvoxid® (in Europe), and Zyvoxam® (in Canada and Mexico), supplied as a ready-to-use sterile isotonic solution for intravenous infusion in single-use, ready-to-use flexible plastic infusion bags of 100mL (200mg) to 300mL (600mg) fills in a foil laminate overwrap. However, plastic infusion bags make a large volume parenteral packaging, difficult to transport and are not suitable for terminal sterilization by autoclaving, which is the preferred method of sterilization by most regulatory bodies.

U.S. Pat. No. 6,989,381 relates to a parenterally deliverable solution wherein cyclodextrins have been used as solubility enhancers through a complex formation with the drug to produce high concentration aqueous formulations of oxazolidinone antibacterial agents. However, cyclodextrins are costly and also amount to the toxicity at the concentrations required to ensure parenteral delivery of an effective amount of an oxazolidinone, such as linezolid.

As will be clear from the disclosure above, there remains a need for concentrated aqueous formulation of antibacterial agent such as linezolid for intravenous administration.

**SUMMARY AND OBJECTIVES OF THE INVENTION**

The invention relates to an aqueous concentrated formulation of linezolid for parenteral use. More particularly, the invention relates to aqueous concentrated formulation of linezolid comprising at least one solubilizer wherein the formulation is preferably administered intravenously.
One aspect of the invention relates to a method of preparing an aqueous concentrated formulation of linezolid comprising dissolving linezolid in a buffered aqueous solution comprising at least one solubilizer.

An object of the invention is to provide aqueous concentrated formulation of linezolid for parenteral use.

Another object of the invention is to provide aqueous concentrated formulation of linezolid comprising at least one solubilizer.

Another object of the invention is to provide a method of preparing an aqueous concentrated formulation of linezolid comprising dissolving linezolid in a buffered aqueous solution comprising at least one solubilizer.

DETAILED DESCRIPTION OF THE EMBODIMENTS OF THE INVENTION

The invention provides aqueous concentrated formulation of linezolid. More particularly, the invention provides aqueous concentrated formulation of linezolid comprising at least one solubilizer wherein the formulation is preferably administered intravenously.

Unless the context clearly requires otherwise, throughout the description and the claims, the words "comprise", "comprising", and the like are to be construed in an inclusive sense as opposed to an exclusive or exhaustive sense; that is to say, in the sense of "including, but not limited to".

The term aqueous concentrated formulation refers to an aqueous solution of linezolid having a concentration of about 3 mg/ml to about 100 mg/ml, preferably about 4 mg/ml to 40 mg/ml, more preferably about 12 mg/ml.
However, it was surprisingly found that concentrated aqueous linezolid formulations can be made by dissolving linezolid in a buffered aqueous solution comprising at least one solubilizer. The use of solubilizer in invention leads to an increase in the solubility of linezolid and in turn reduces the overall volume of the final composition so that it can be filled and packaged in a vial. This makes the product easy to transport and sterilization.

In a preferred embodiment, the invention provides an aqueous concentrated formulation of linezolid comprising at least one solubilizer.

In a still preferred embodiment of the invention, the solubilizer described herein can be a non-ionic hydrophilic surfactant.

Thus, the non-ionic hydrophilic surfactant which can be used in the context of the invention may be one or more polyethylene glycol mono- and di-fatty acid ester, for example, polyethylene glycol dicaprylate, polyethylene glycol dilaurate, polyethylene glycol hydroxystearate, polyethylene glycol isostearate, polyethylene glycol laurate, polyethylene glycol ricinolate, polyethylene glycol stearate, and the like.

More preferably, the non-ionic hydrophilic surfactant is polyethylene glycol hydroxystearate which is commercially available as Solutol® HS 15. Solutol® HS 15, a water-soluble non-ionic surfactant used for pharmaceutical purposes, is a mixture of 70% lipophilic molecules consisting of polyglycol mono- and diesters of 12-hydroxystearic acid and 30% hydrophilic molecules consisting of polyethylene glycol.

Solutol® HS 15 meets the requirements of an effective modern solubilizer for parenteral use owing to its high solubilizing capacity and low toxicity. The Solutol® HS 15 is present at a concentration effective to enhance the solubility of the oxazolidinone, for example at a concentration of about 5% to about 75%.
More preferably at a concentration of about 12.5% to about 50% of the composition.

The aqueous concentrated formulation of linezolid according to the invention comprises water or a water-based medium as the liquid medium. Apart from water, the liquid medium or vehicle may also comprise conventional physiologically acceptable auxiliary substances known to a person skilled in the art. These physiologically acceptable auxiliary substances are preferably selected from a group consisting of pH-regulators, buffers, regulators for adjusting osmolality and the like.

Thus, pH adjusting agents which can be used in context of the invention may be, acids such as acetic, boric, citric, lactic, phosphoric and hydrochloric acids; bases such as sodium hydroxide, sodium phosphate, sodium borate, sodium citrate, sodium acetate, sodium lactate, tris hydroxymethylaminomethane and the like.

Thus, buffer systems which can be used in context of the invention may be, for example, sodium acetate or potassium acetate, a phosphoric acid/monopotassium phosphate/citric acid combination, monosodium phosphate or monopotassium phosphate or an aqueous solution of glycine/strong acid such as hydrochloric acid, citric acid/sodium citrate or potassium hydrogen phthalate.

Such acids, bases and buffers are included in an amount required to maintain pH of the composition in a physiologically acceptable range, particularly where the composition is intended for intravenous delivery.

In order to minimise or completely rule out the risk of cell and tissue damage on intravenous administration of the dosage form, the osmolality i.e. the tonicity of the dosage form according to the invention is preferably adjusted such that it is isotonic or at least approximately isotonic to physiological osmolality. Preferred regulators for adjusting osmolality which can be used in context of the invention
may be water-soluble, physiologically acceptable compounds such as inorganic salts, for example alkali metal salts, preferably sodium chloride, sugars, for example sucrose or dextrose, sugar alcohols, for example mannitol, or polyalkylene glycols, for example polyethylene glycols.

Other pharmaceutically acceptable excipients can also be included as desired in compositions of the invention, having functions conventional in the art and in amounts consistent with those functions.

In another embodiment, the aqueous concentrated formulation of linezolid can be prepared by a process which includes admixing of the ingredients, with agitation, if required, involving the steps of:

a) Preparing a buffered aqueous solution comprising at least one solubilizer;
b) Adding linezolid to the said solution;
c) Heating the solution to dissolve linezolid completely;
d) Making the final volume with the water for injection.

The aqueous concentrated formulation of linezolid of the invention can be filled and packaged in vials.

Various containers are known to hold aqueous solutions to be administered IV to a patient. The most common IV solution containers are glass and plastic bottles and plastic bags. Containers suitable for injection in connection with the invention refers to containers which do not interact physically or chemically with the preparation for injection in any manner to alter the strength, quality, or purity beyond the official requirements under the ordinary or customary conditions of handling, shipment, storage, sale and use.

Suitable containers in accordance with the invention are for example made of glass. Particularly suitable are type 1 glass container. In one embodiment of the
invention, the container is a clear glass vial such as SCHOTT Type I plus, characterized by the purity and inertness of a quartz-like inner surface (100% SiO2 coating), a thickness of 100 - 200 nm which fulfills the criteria of type I glass containers according to European Pharmacopoeia, United States Pharmacopoeia and Japanese Pharmacopoeia. These vials with excellent barrier properties can be washed, autoclaved, sterilized, depyrogenated, filled, closed and inspected just like standard containers. In a further embodiment, the product of the present invention can be packed in non glass containers such as cyclic olefin copolymer (COC) containers e.g SCHOTT TopPac vials offer the highest purity and transparency comparable to glass. Due to excellent barrier properties, high chemical resistance and breakage resistance, COC vials are an excellent alternative to glass. They have a superior moisture barrier compared to HOPE or PP and can be sterilized.

The container for injection according to the invention is closed or sealed with a suitable stopper in such a manner as to prevent contamination or loss of content. In a preferred embodiment, the stoppers which can be used in the present invention include coated or uncoated chlorobutyl or fluoro butyl stoppers. The examples of closures which can be used are Fluorotech stoppers. Preferably the vials and stoppers are sterile and filling is conducted under aseptic conditions.

The formulation prepared as above can be easily diluted with any of the commonly available infusion solutions like Dextrose Injection, Sodium Chloride Injection, Lactated Ringer's Injection or others to the desired concentration prior to administration. Even Water for Injection can also be used to prepare the dilutions.

Sterilization methods that may be used in the present invention, include, but are not limited to, filtration sterilization, autoclaving, aseptically preparing and dispensing in the sterile containers or combination of one or more said methods.
The moist heat sterilization is more preferred at lower temperature to avoid the degradation during sterilization. In a preferred embodiment, the product of the present invention can be sterilized by moist heat sterilization or by aseptic filtration. The aseptic filtration is the most preferred method of the sterilization, for example solution is sterilized by passing through one or more sterilizing filters, and is then metered into one or more vials.

In a further embodiment of the invention, there is provided a pharmaceutical kit comprising the aqueous concentrated formulation of linezolid comprising at least one solubilizer and sterile infusion solutions Dextrose Injection, Sodium Chloride Injection, Lactated Ringer’s Injection, or Water for Injection.

An appropriate dosage, frequency and duration of administration, i.e., treatment regimen, to be used in any particular situation will be readily determined by one skilled in the art without undue experimentation, a daily dose for a human subject will typically be about 100 mg to about 1200 mg of linezolid, administered in a composition of the invention.

The invention is illustrated herein with particular reference to linezolid, and it will be understood that any other oxazolidinone antimicrobial drug can, if desired, be substituted in whole or in part for linezolid, with appropriate adjustment in concentration and dosage ranges, in the compositions and methods herein described.

EXAMPLES
The following Examples illustrate aspects of the invention but are not to be construed as limitations.

Example 1
Linezolid solubility was studied by dissolving the active in the different concentrations of solutol HS 15 at 25°C. The results are indicated below in Table
1. Saturation solubility of linezolid in pure water at pH 7 was determined separately to be 3mg/ml.

Table 1

<table>
<thead>
<tr>
<th>Solutol concentration (%)</th>
<th>Linezolid solubility (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.5</td>
<td>6.1025</td>
</tr>
<tr>
<td>25</td>
<td>8.2875</td>
</tr>
<tr>
<td>50</td>
<td>12.5195</td>
</tr>
</tbody>
</table>

Example 2

The aqueous concentrated formulation according to invention was prepared by the process wherein sodium citrate, citric acid, dextrose and Solutol® HS15 are added to water for injection and stirred until dissolved. Linezolid was added to this buffered solution with agitation. The solution was further heated up to 70-80° C until linezolid fully dissolved. The pH of the solution was measured and adjusted if necessary. Final volume is made up with the water for injection. The mixture is filtered, filled into sterile vials.

Table 2

<table>
<thead>
<tr>
<th>Linezolid Injection Concentrate</th>
<th>Mg/vial (50 ml)</th>
<th>Mg/vial (50 ml)</th>
<th>Mg/Vial (100 ml)</th>
<th>Mg/Vial (100 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ingredients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Linezolid</td>
<td>600</td>
<td>600</td>
<td>1200</td>
<td>1200</td>
</tr>
<tr>
<td>2 Sodium citrate dihydrate</td>
<td>492</td>
<td>492</td>
<td>984</td>
<td>984</td>
</tr>
<tr>
<td>3 Citric acid anhydrous</td>
<td>255</td>
<td>255</td>
<td>510</td>
<td>510</td>
</tr>
<tr>
<td>4 Dextrose monohydrate</td>
<td>2512</td>
<td>2512</td>
<td>5024</td>
<td>5024</td>
</tr>
<tr>
<td>5 Solutol® HS 15</td>
<td>12500</td>
<td>25000</td>
<td>25000</td>
<td>50000</td>
</tr>
<tr>
<td>6 HCl/ NaOH</td>
<td>q.s. To pH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 Water for Injection</td>
<td>q.s to 50 ml</td>
<td>q.s to 50 ml</td>
<td>q.s to 100 ml</td>
<td>q.s to 100 ml</td>
</tr>
</tbody>
</table>

Total volume (ml) containing 600mg dose

<table>
<thead>
<tr>
<th>Mg/vial (50 ml)</th>
<th>Mg/vial (50 ml)</th>
<th>Mg/Vial (100 ml)</th>
<th>Mg/Vial (100 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>50</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

The very substantial reduction in volume of IV solution providing a 600 mg dose of linezolid, permitted by addition of solutol, is clearly seen in Table 2 above.
Thus, the above-listed additives should be taken as merely exemplary, and not limiting, of the types of additives that can be included in compositions of the invention.

While the invention has been described in detail with respect to specific embodiments thereof, it will be apparent that numerous modifications and variations are possible without departing from the scope of the invention.
WE CLAIM

1. An aqueous concentrated antibacterial formulation of linezolid comprising at least one solubilizer.

2. The aqueous concentrated antibacterial formulation according to claim 1, which comprises about 3 to about 100 mg/ml of concentration of linezolid.

3. The aqueous concentrated antibacterial formulation according to claim 1, which comprises about 4 to about 40 mg/ml of concentration of linezolid.

4. The aqueous concentrated antibacterial formulation according to claim 1, which comprises about 12 mg/ml of concentration of linezolid.

5. The aqueous concentrated antibacterial formulation according to claim 1, wherein at least one solubilizer is a non-ionic hydrophilic surfactant.

6. The aqueous concentrated antibacterial formulation according to claim 5, wherein non-ionic hydrophilic surfactant is in the concentration range of about 5% to about 75% of the formulation.

7. The aqueous concentrated antibacterial formulation according to claim 6, wherein the solubilizer is present at a concentration of about 12.5% to about 50% of the formulation.

8. The aqueous concentrated antibacterial formulation according to claim 5, wherein said non-ionic hydrophilic surfactant is selected from polyethyleneglycol mono- and di-fatty acid ester which include polyethyleneglycol dicaprylate, polyethyleneglycol dilaurate,
polyethyleneglycol hydroxystearate, polyethyleneglycol isostearate, polyethyleneglycol laurate, polyethyleneglycol ricinolate, polyethyleneglycol stearate and the like

9. The aqueous concentrated antibacterial formulation according to claim 8, wherein said non-ionic hydrophilic surfactant is polyethyleneglycol hydroxystearate which is commercially available as Solutol® HS15.

10. A method of preparing an aqueous concentrated antibacterial formulation of linezolid comprising
a) Preparing a buffered aqueous solution comprising at least one solubilizer
b) Adding linezolid to the said solution
c) Heating the solution to dissolve linezolid completely
d) Making the final volume with the water for injection

11. A method of treating an infection by gram-positive bacteria in a mammal in need of such treatment, comprising intravenously administering the aqueous concentrated antibacterial formulation according to claim 1 to such mammal.