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(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING PEMETREXED TOGETHER WITH MONOTHIOGLYCEROL L-CYSTEIN OR THIOGLYCOLIC ACID

(57) Abstract: The present invention provides a pharmaceutical composition comprising pemetrexed; at least one antioxidant selected from the group consisting of monothioglycerol, L-cysteine, and thioglycolic acid; and apharmaceutically acceptable excipient. The pharmaceutical formulation is suitable for liquid parenteral administration.

PHARMACEUTICAL COMPOSITION COMPRISING PEMETREXED TOGETHER WITH MONOTHIOGLYCEROL L-CYSTEINE OR THIOGLYCOLIC ACID

The present invention relates to a liquid composition comprising the known compound pemetrexed and an antioxidant; which liquid composition is stable and pharmaceutically elegant.

Certain folic acid antimetabolites are known to be antineoplastic agents. These compounds inhibit enzymatic conversion involving metabolic derivatives of folic acid. One such compound, described by United States Patent 5, 344,932, is currently being developed for potential use as a pharmaceutical agent. This compound, known as "pemetrexed", is most desirably formulated into a concentrated liquid for administration as an infusion dosage form. Pemetrexed Disodium is the active ingredient in the anticancer drug ALIMTA now in clinical development by Eli Lilly and Company.

The formulation teachings of the US Patent 5,344,932 provide that the compounds claimed therein can be administered parenterally.

A ready to use, stable, ready to reconstitute solution that could be stored at room temperature is particularly desired for a pharmaceutical such as pemetrexed, wherein such ready to use formulation provides easier, safer handling, storage, and distribution. It is particularly desirable if the stable formulation can be prepared without the use of freeze drying techniques. The desired liquid formulation can offer enhanced safety for caregiver handling of the cytotoxic materials. Further, a stable, ready to use formulation is more acceptable to the customer.

It was discovered that a simple, isotonic saline solution of pemetrexed is not pharmaceutically acceptable for commercial purposes due to degradation of the solution to form unacceptable related substances. It has now been discovered that pharmaceutically acceptable, concentrated, ready to use, liquid solutions of pemetrexed may be prepared when the formulation includes certain antioxidants, including monothioglycerol, L-cysteine, and thioglycolic acid. Other antioxidants

were studied; however, surprisingly, of the antioxidants studied, these provided the desired formulation characteristics described herein.

The formulation can exhibit acceptable stability, retain a pharmaceutically desirable appearance, maintain the desired enatiomeric stability, and fulfil the health care provider's desire for a stable, ready to use liquid formulation. Additionally, the formulation may be suitable for parenteral dosage, can be delivered to the health care provider in a clear vial and can be stored at temperatures above 4 degrees Celsius in a highly concentrated state.

One embodiment can addresse the need for a pharmaceutically stable liquid pemetrexed formulation having both color stability and acceptable shelf life stability with regard to retaining the solution dosage form and avoiding unacceptable degradation to undesired related substances. Additionally, the formulations can be diluted to the desired administration concentration by the health care provider. Finally, the formulations may not require the addition of any preservative, other than the antioxidant, in order to retain the desired concentration and stability.

An aspect of the present invention provides a pharmaceutical composition comprising:

a) pemetrexed;

b) at least one antioxidant selected from:

i) monothioglycerol,

ii) L-cysteine, and

iii) thioglycolic acid; and

c) a pharmaceutically acceptable excipient.

The three antioxidants can be uniquely effective for the claimed formulation. Surprisingly, common antioxidants, such as sodium metabisulfite, ascorbic acid, sodium EDTA, monoethanolamine gentisate, sodium formaldehyde sulfoxylate, sodium bisulfite, did not provide the desired formulation characteristics.

An especially preferred antioxidant can be monothioglycerol.

The concentration of monothioglycerol may most preferably be from about 1 part per million to 8.0 mg/ml, which concentration may be optimized for a given formulation based on the oxygen concentration contacting the formulation. The concentration of monothioglycerol may preferably be at least 0.6 mg/ml, more preferably at least 0.8 mg/ml, especially preferably is at least 1.0 mg/ml. The concentration of monothioglycerol may preferably be up to 6 mg/ml, more preferably up to 5mg/ml, and most preferably is up to 3 mg/ml.

It may be preferred that the concentration of monothioglycerol may be from 0.6 mg/ml to 6 mg/ml. More preferably, the concentration of monothioglycerol may be from 0.8 mg/ml to 5.0 mg/ml. It is especially preferred that the concentration of monothioglycerol may be at least 1.0 mg./ml. An especially desired concentration may be from 1.40 mg/ml to 3.0mg/ml. A further desired concentration may be from 2 mg/ml to 3 mg/ml. A further preferred concentration of monothioglycerol may be from 1.2 mg/ml to 2.4mg/ml.

In general, the concentration of monothioglycerol, L-cysteine or Thioglycolic acid may be most preferably from 1 part per million to 8.0 mg/ml, which concentration may be optimized for a given formulation based on the oxygen concentration contacting the formulation. L-cystine or thioglycolic acid are often most effective at a higher pH. It may be preferred that the concentration of monothioglycerol, L-cysteine or Thioglycolic acid may be from 1.0 mg/ml to 6 mg/ml. More preferably, the concentration of monothioglycerol, L-cysteine or Thioglycolic acid may be from 0.8 mg/ml to 5.0 mg/ml. It may especially be preferred that the concentration of monothioglycerol, L-cysteine or Thioglycolic acid may be at least 1.0mg./ml. An especially desired concentration for monothioglycerol, L-cysteine or Thioglycolic acid may be from 1.40 mg/ml to 3.0 mg/ml. A further desired concentration may be from 2 mg/ml to 3 mg/ml. A further preferred concentration of monothioglycerol, L-cysteine or Thioglycolic acid may be from 1.2 mg/ml to 2.4 mg/ml. It may be preferred to have a concentration of from 0.1 mg/ml to 7mg/ml. When the antioxidant is monothioglycerol or L- cysteine, the preferred concentration range may be from 0.1 mg/ml to 10.0mg/ml.

The concentration of L-cysteine may preferably be greater than 0.1 mg/ml, more preferably greater than 0.5 mg/ml and most preferably greater than 1 mg/ml.

The concentration of L-cysteine may preferably less than 10 mg/ml, more preferably less than 8 mg/ml, and most preferably less than 6 mg/ml.

The concentration of thioglycolic acid may preferably greater than 0.1 mg/ml, more preferably greater than 0.5 mg/ml and most preferably greater than 1 mg/ml.

The concentration of thioglycolic acid may preferably less than 10 mg/ml, more preferably less than 8 mg/ml, and most preferably less than 6 mg/ml.

Additionally, combinations of the three antioxidants, selected from monothioglycerol, L-cysteine and thioglycerol, may also be used.

The concentration of pemetrexed may preferably be from 20 to 100 mg/ml. It may be especially preferred that the pemetrexed concentration may be from 30mg/ml to 70mg/ml. A further preferred embodiment may be when the pemetrexed concentration is from 35 mg/ml to 50 mg/ml. A further preferred embodiment may be a pemetrexed concentration of from 38mg/ml to 44 mg/ml. An especially desired concentration of pemetrexed may be 40 mg/ml.

As used herein, the term "pemetrexed" can refer to the stable salts, acids and free base forms thereof. The term can include, for example, the free acid, the pharmaceutically acceptable alkali metal, alkaline earth metal, non-toxic metal, ammonium, and substituted ammonium salts, such as for example, the sodium, potassium, lithium, calcium, magnesium, aluminum, zinc, ammonium, trimethylammonium, triethylammonium, monoethanolammonium, triethanolammonium, pyridinium, and substituted pyridinium salts. The substituted ammonium salts can be one especially preferred group of salts.

As used herein, the term "pharmaceutically acceptable excipient" can mean a pharmaceutically acceptable formulation carrier, solution or additive to enhance the formulation characteristics. Such additives are well known to the skilled artisan. While any pharmaceutically acceptable diluent is suitable, for example sodium chloride or mannitol, an especially preferred

excipient for parenteral administration can be saline solution.

The disodium salt of pemetrexed may be particularly preferred for use in the present formulation.

The pH of the formulation may most preferably be from 5.5 to 12. The formulation may more preferably be from pH 7 to 11. It may be especially desired that the pH of the formulation may be from 8.0 to 9.0. It is further preferred that the pH may be from 8 to 9 when the antioxidant is monothioglycerol. When the antioxidant is L-cysteine or thioglycolic acid or any salt form thereof, then the preferred pH may be 8 to 10. The artisan will appreciate that combinations of these antioxidants can provide new preferred pH ranges. Standard modifications of the composition can provide compositions of various pH within the contemplation of this invention.

It may be generally preferred that the process for preparing the formulation includes the use of a purge of an inert gas. Such inert gases can, for example, be nitrogen, argon, and the like. The use of an isolator to maintain low oxygen conditions may be desirable, but may not be required for storage of the present formulation.

While any pharmaceutically acceptable stopper may be used to seal the vial containing the formulation, it may be preferable to seal the vial with a stopper which is siliconized. A sterlized teflon coated stopper may be desired for sealing the storage vial.

Most pharmaceutically acceptable liquid formulation vials or containers can be used to dispense the claimed formulation. It may be desired that the containing vessel minimizes the concentration of oxygen that reaches the formulation. Thus, vials or ampules may be especially desired vessels for the formulation. A sealed vial may be especially desired for commercial purposes in most countries.

The artisan will appreciate that the use of depyrogenated prewashed vials may be desired for the storage of a sterile liquid formulation that is intended for parenteral use. The vial may be colored; however, a clear vial can be acceptable for storage of the formulation. Any pharmaceutically acceptable material may be used to make the formulation container; however, glass may be an especially preferred container material. A

glass vial may be a preferred container. Other packaging materials for parenterals like plastic vials may be preferred options as well. For example, plastic vials may be useful.

It may be desirable to protect the bulk solution from light during the process of preparing the formulation; however, such protection may not be required for the formulation.

The resulting formulation can be sterlized using methods known to the artisan.

Such sterilisation methods may include, for example, sterile filtration or heating. It can be especially beneficial that the presently claimed formulation is stable during heat sterilization.

It may be preferred that the headspace of the vial contains less than about 8% v/v Oxygen; however, the headspace of the vial may contain more than 8% oxygen if other conditions of the formulation are appropriately adjusted. It may be more preferred that the headspace of the vial contains from 2% to 5% Oxygen. It may be especially preferred that the headspace contains from 3% to 5% Oxygen. It may be further preferred that the headspace contains less than about one ppm oxygen. Also preferably, the headspace oxygen content may be less than about 0.1% v/v oxygen. A preferred condition can be that the headspace of the vial is less than about 1% oxygen.

The headspace of the vial can be adjusted to minimize the formulation contact with oxygen. It may be generally desired that the headspace may not be more than about 1/3 of the total volume of the container, with the fill taking at least about 2/3 of the total volume of the container. For example, it may be preferred that 5 ml of fill be used for a 7.5 ml vial. If a greater headspace ratio to fill is desired, then the concentration of the antioxidant may be adjusted as necessary.

The pharmaceutical formulation may be suitable for both human clinical use and veterinarian use for animals.

Pemetrexed can be prepared using the processes described in United States Patent 5,473,071. Compositions of pemetrexed are useful to treat cancer, as described in the 5,344,932 patent as well as in Seminars in Oncology, Vol. 26, No. 2, Supplement 6 (April 1999).

Monothioglycerol can be commercially available from suppliers of fine chemicals which are well known to the artisan. To further clarify, Monothioglycerol is Chemical Abstracts number: 96-27-5.

Likewise, L-cysteine (CAS:52-90-4), L-cysteine hydrochloride monohydrate (CAS: 7048-04-6), L-cysteine hydrochloride monohydrate anhydrous (CAS: 52-89-1) and thioglycolic acid (CAS: 68-11-1) can readily be obtained from suppliers of fine chemicals.

Description of Preferred Embodiments.

The Present invention is seen more fully by the examples given below.

Example 1

Pemetrexed, was prepared as a 40 mg/ml solution in water. Monothioglycerol was prepared as a 2.4 mg/ml solution using water for injection. The pH of the monothioglycerol solution was adjusted to 8.5 using sodium hydroxide.

The bulk solution was protected from light. The solution was purged with nitrogen for twenty minutes and then sterile filtered. The formulation was dispensed into prewashed, depyrogenated vials and then stoppered with a prewashed, presterilized teflon coated stopper. Caps were attached using a crimper. The sterile filtration and dispensing steps were conducted using a nitrogen isolator (5% v/v Oxygen).

The solution filled vials were heat sterilized.

Example 2

A pharmaceutical composition was prepared substantially as described herein by Example 1, except that the antioxidant was 0.03% L-Cysteine and the pemetrexed concentration was four percent (4%).

Example 3

A pharmaceutical composition was prepared substantially as described herein by Example 1, except that the antioxidant was 0.03% Thioglycolate and the pemetrexed concentration was four percent (4%).

Claims

1. A pharmaceutical composition comprising:
a) pemetrexed;
b) at least one antioxidant selected from:
i) monothioglycerol,
ii) L-cysteine, and
iii) thioglycolic acid; and
c) a pharmaceutically acceptable excipient.

2. A pharmaceutical composition as claimed by Claim 1 wherein the composition is a liquid formulation suitable for parenteral administration.

3. A pharmaceutical composition as claimed by any one of Claims 1 and 2 wherein pemetrexed is the disodium salt.

4. A pharmaceutical composition as claimed by any one of Claims 1 to 3 wherein the antioxidant is monothioglycerol.

5. A pharmaceutical composition as claimed in any one of Claims 1 to 4 wherein the monothioglycerol concentration is from 1 part per million to 8 milligrams per milliliter.

6. A pharmaceutical composition of Claim 5 wherein the monothioglycerol concentration is from 1 mg/ml to 6 mg/ml.

7. A pharmaceutical composition of Claim 6 wherein the monothioglycerol concentration is from 1 mg/ml to 2.5 mg/ml.

8. A pharmaceutical composition of Claim 4 wherein the monothioglycerol concentration is from 0.5 mg/ml to 3 mg/ml.

9. A pharmaceutical composition as claimed by any one of Claims 1 to 3 wherein the antioxidant is L-cysteine.

10. A pharmaceutical composition of Claim 9 wherein the L-cysteine concentration is from 1 part per million to 8 mg/ml.

11. A pharmaceutical composition of Claim 10 wherein the L-cysteine concentration is from 1 mg/ml to 6 mg/ml.

12. A pharmaceutical composition of Claims 1 to 3 wherein the antioxidant is thioglycolic acid.

13. A pharmaceutical composition of Claim 12 wherein the thioglycolic acid concentration is from 1 part per million to 8 mg/ml.

14. A pharmaceutical composition of Claim 13 wherein the thioglycolic acid concentration is from 0.1 mg/ml to 6 mg/ml.

15. A pharmaceutical composition of Claim 4 wherein the monothioglycerol concentration is from 0.1 mg/ml to 10 mg/ml.

16. A pharmaceutical composition of Claim 15 wherein the monothioglycerol concentration is from 0.1 mg/ml to 6 mg/ml.

17. A pharmaceutical composition of Claim 9 wherein the L-cysteine is from 0.1 mg/ml to 10 mg/ml.

18. A pharmaceutical composition of Claim 17 wherein the L-cysteine is from 0.1 mg/ml to 6 mg/ml.

19. A pharmaceutical composition of Claim 12 wherein the thioglycolic acid is from 0.1 mg/ml to 10 mg/ml.

20. A pharmaceutical composition of Claim 19 wherein the thioglycolic acid is from 0.1 mg/ml to 6 mg/ml.