

humidities, to test the integrity and durability of the packaging system. As packaged for clinical use, 20 ml vials have been dry-filled with 110 mg of ethylene oxide sterilized artesunic acid, stoppered, and sealed. Stability studies at Knoll have shown at least two years stability for bulk artesunic acid stored under nitrogen @ 25° C.

Example 2

Preclinical Toxicology

[0076] Tests of the dry-filled artesunate formulation were used in the GLP 14-day dog toxicity study. A concentrated formulation of 50 mg AS/ml was developed and manufactured for a 14-day cGLP toxicity study in dogs. The dry-filled artesunic acid formulation used in the GLP 14-day dog toxicity study was confirmed to be of high purity by independent analysis. The artesunic acid content weights, calculated from determining the mg of artesunic acid/mL in reconstituted samples, met the requirements set forth in USP Article <905> and ranged between 501 to 519 mg/vial.

[0077] The potential toxicity of GMP artesunate of the invention was tested in beagle dogs. The artesunate was administered daily by rapid intravenous infusion (over 4 to 6 minutes) for 14 days. Four groups consisting of 4 dogs/sex/group were treated daily with doses of artesunate at 10, 20, 35, or 50 mg/kg/day at dose volumes of 1 mL/kg. One group of 4 dogs/sex received sterile 0.3 M phosphate buffer (control article) and served as the control group. The study was divided into two parts. After 14 doses, 2 dogs/sex/group were necropsied on study day (SD) 15. The remaining two dogs/sex/group were allowed a 2-week treatment-free recovery period and were necropsied on study day 29. Measurements included survival, clinical observations, body weights, electrocardiography, hematology, clinical chemistry, coagulation parameters, gross pathology, organ weights, and histopathology (Wu and Senate, 2004). Intravenous doses of artesunate up to and including 50 mg/kg/day did not result in test article-related effects on mortality, clinical observations, body weights, body weight gains, food consumption, electrocardiographic output, clinical chemistry and coagulation, gross pathology, organ weights, and histopathology. During the course of the study, erythema, diarrhea, emesis, mucoid feces, and soft feces were observed sporadically in both control and test article-treated groups, and were not considered to be test article-related. Intravenous administration of artesunate at doses of 20, 35, or 50 mg/kg/day for 14 days in beagle dogs resulted in lowered red blood cell parameters (RBC, HGB, HCT, and RETIC) measured on study day 15. The lower reticulocyte counts suggested that there was not a regenerative response to the lower RBCs. The lowered red blood cell parameters found on study day 15 were not present on study day 29.

[0078] Based on the results of this study, artesunate, when administered intravenously for 14 days at doses up to and including 50 mg/kg/day, did not result in any other test article-

related adverse effects except on the measure hematology. At doses of 20 mg/kg/day and above, intravenous administration of artesunate for 14 days resulted in a transient test article-related effect on red blood cell parameters, including RBC, HGB, HCT, and RETIC.

[0079] Having now fully described the invention, it will be apparent to one of ordinary skill in the art that many changes and modifications can be made thereto without departing from the spirit or scope of the invention as set forth herein.

1-18. (canceled)

19. A method for the production of an artesunic acid product that has a shelf life of two years and that does not produce CO₂ upon dissolution comprising the steps of:

- a. sterilizing artesunic acid powder;
- b. dissolving said sterilized artesunic acid powder in physiologically acceptable buffered solution to produce an injectable formulation.

20. The method of claim 19, wherein said physiologically acceptable buffered solution is sodium phosphate.

21. The method of claim 20, wherein the sodium phosphate solution has an average of about 0.30±0.05 M, and a pH of about 8.0±0.3.

22. The method of claim 19, wherein said artesunic acid product is 320 for a 10 mg/ml artesunic acid solution.

23. An artesunic acid formulation prepared by the method of claim 19.

24. A kit for making an artesunic acid formulation comprising: a first vial containing artesunic acid powder that has been sterilized with ethylene oxide and purged with nitrogen to remove water vapor and a second vial containing sodium phosphate solution of an average of about 0.30±0.05M at an average pH of about 8.0±0.3, wherein when said sodium phosphate solution is mixed with said artesunic acid in said first vial, a sterile artesunic acid solution is formed with no clumping or CO₂ production upon dissolution of the artesunic acid.

25. A method for treating a malaria patient comprising the steps of:

- a) preparing a formulation of sterile artesunic acid solution by the method of claim 19; and
- b) administering said sterile artesunic acid formulation to said patient by intravenous or intramuscular injection.

26. A method of preparing a single dose of artesunic acid for parenteral or intravenous administration comprising: mixing 11 mL sterile physiologically acceptable buffered solution with 110 mg artesunate.

27. The method of claim 26, wherein said physiologically acceptable buffered solution is sodium phosphate.

28. The method of claim 26, wherein said intravenous injection is via a drip bag.

29. The method of claim 26, wherein said sterile artesunic acid solution is given at a dose of 1-8 mg/Kg body weight for intravenous injection one to two times per day for three days.

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