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(54) Title: COMPOSITIONS AND METHODS FOR THE ADMINISTRATION OF δ-AMINOLEVULINIC ACID AND PHARMACEUTICAL EQUIVALENTS THEREOF

(57) Abstract

A pharmaceutical composition of increased stability, which comprises ALA or pharmaceutical equivalents thereof and a pharmaceutically acceptable, flexible, finite carrier suitable for administration to the skin or other dermal membrane of a mammal, optionally containing a stabilizing amount of an organic weak proton donor or saccharide containing substance. The pharmaceutically acceptable carrier in solid formulation can be a skin patch, many forms and types of which are known and used in the art. It is preferable that the composition be anhydrous. The formulations appear to improve the fluorescence produced after exposing treated skin to activating light, as compared with the fluorescence produced with ALA in a fluid carrier. In particular, the pattern of fluorescence is more even and uniform over the area of application than with topical creams or salves and may provide increased fluorescence.

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COMPOSITIONS AND METHODS FOR THE ADMINISTRATION OF δ-AMINOLEVULINIC ACID AND PHARMACEUTICAL EQUIVALENTS THEREOF

Cross-Reference to Related Applications

This application is a continuation-in-part of PCT/US94/09466, filed August 27, 1994, which is a continuation-in-part of Serial No. 08/112,330 filed August 27, 1993, which is a continuation-in-part of PCT/US92/01730, filed February 27, 1992, which is a continuation-in-part of U.S. Application Serial No. 07/813,196, filed December 23, 1991, now U.S. Patent No. 5,234,957, which is a continuation-in-part of U.S. Patent Application Serial No. 07/661,827, filed February 27, 1991 and now abandoned. All of the foregoing applications are hereby incorporated by reference.

Background of the Invention

5-Aminolevulinic acid, also referred to as δ-aminolevulinic acid or 5-amino-4-oxopentanoic acid, is referred to herein as "ALA". ALA has been known for over 40 years to be a precursor in the metabolic pathway to heme in humans and to chlorophyll in plants. Until the past ten years ALA has been of limited usefulness, namely, use limited to porphyrin research. In 1984, ALA was proposed for use as a photodynamic herbicide. It has been discovered recently that ALA can be used by various routes of administration to detect and treat certain conditions involving rapidly metabolizing cells, namely hyperproliferative cells. It is especially useful in the treatment of malignant and non-malignant abnormal growths.

ALA has been administered by various routes known for use in drug administration, but especially by topical

application to the skin and epithelium of various body cavities. Application of ALA results in the selective accumulation of clinically significant amounts of protoporphyrin IX, another precursor in the metabolic pathway to heme. Activation of protoporphyrin IX by light, depending on the wavelength of the light, will cause the protoporphyrin IX either to fluoresce (which can be used as the basis of a detection method), or to decompose (which can be used as the basis of treatment for cells that need to be removed).

ALA previously has been used in clinical testing on humans and other mammals in aqueous and non-aqueous fluid vehicles such as creams (oil in water emulsions) and lotions for application to the skin and orally for the diagnosis and treatment of skin cancers. ALA has been used in clinical studies in aqueous solution for application to the endometrial cavity.

ALA has been reported to inhibit degradation of the drug calcitonin by the nasal mucosa peptides in U.S. 5,026,825 . Preparations in the examples of that patent show a combination of calcitonin and ALA in aqueous solutions containing one or more of benzalkonium chloride, citric acid, sodium citrate, hydrochloric acid, sodium acetate and acetic acid. The organic acids and their salts appear to be used as buffers, to adjust the pH of the resulting solution to about 4.

ALA has a tendency to decompose in a wide variety of vehicles used in clinical testing including both water containing vehicles, anhydrous fluid vehicles and water and oil emulsions. In general, the lower the pH of the fluid vehicle, the more rapid the degradation. For example, addition of about 10% by weight ALA in the form the hydrochloride salt into an alkaline solution, left at room temperature, results in almost complete degradation in about one week.

Precursors or prodrugs of ALA have been reported for use in conditions similar to that as reported for ALA. The Norwegian Radium Hospital Research Foundation's PCT application No. WO 95/07077 published March 16, 1995 ("precursors") and *Peng et al.* Abstract, American Society of Photobiology Annual Meeting, 1995 Budapest.

The decomposition occurring with fluid preparations, such as water and ethanol, reported in the scientific literature with use of ALA patients, is sufficient to preclude the use of ALA in a product to be distributed in normal, existing channels for the supply of pharmaceuticals. Many studies have been performed without success in an attempt to stabilize ALA, with respect to extending the stability of the chemical in a fluid, including use of an aqueous solution containing certain antioxidants such as ascorbic acid and sodium bisulfite. Thus, there remains a need for a storage stable composition comprising ALA in a form suitable for administration to a patient.

Summary of the Invention

The invention relates to a pharmaceutical composition of increased stability, which comprises ALA and a pharmaceutically acceptable, flexible, finite carrier suitable for administration to the skin or other dermal membrane of a mammal, optionally containing a stabilizing amount of an organic weak proton donor or a saccharide.

The pharmaceutically acceptable carrier in solid formulation for topical delivery to the skin is desirably a skin patch, many forms and types of which are known and used in the art. It is preferable that the composition be prepared without - and essentially contain no - water. Not only are these formulations using a topical solid carrier stable after prolonged storage, but use of the formulations appear to improve the fluorescence produced

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