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(54) Title: PHARMACEUTICALLY ACCEPTABLE COMPOSITION COMPRISING AN AQUEOUS SOLUTION OF PACLITAXEL AND ALBUMIN

(57) Abstract

An optically clear, pharmaceutically acceptable aqueous composition comprising paclitaxel or a derivative thereof, serum albumin and a pharmaceutically acceptable vehicle, wherein the composition comprises no more than 10 % organic solvent and has a pH of about 3.0 to about 4.8, is described. The serum albumin can be fatted or defatted, and the composition can optionally be lyophilized or optionally lyophilized and reconstituted. At least 70 % of the paclitaxel is bound to serum albumin, the ratio of paclitaxel to albumin is at least about 1:5, and the concentration of paclitaxel is at least about 25 μg/ml. Methods of making and using this composition are also provided.

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PHARMACEUTICALLY ACCEPTABLE COMPOSITION COMPRISING AN AQUEOUS SOLUTION OF PACLITAXEL AND ALBUMIN

CROSS-REFERENCE TO RELATED APPLICATIONS

(Not Applicable)

STATEMENT OF RIGHTS TO INVENTIONS MADE UNDER FEDERALLY-SPONSORED RESEARCH

(Not Applicable)

TECHNICAL FIELD

The present invention relates generally to aqueous formulations of paclitaxel and methods of use thereof. More specifically, it pertains to pharmaceutical compositions comprising paclitaxel (Ptx) or a derivative thereof and serum albumin or a fragment thereof, particularly human serum albumin, and more particularly recombinant human serum albumin, and a physiologically acceptable vehicle; methods of preparation of such pharmaceutical compositions; and methods of use thereof. The vehicle can comprise an organic solvent, and the composition lacks a toxic emulsifier such as Cremophor EL® (polyoxyethylated castor oil).

BACKGROUND OF THE INVENTION

Paclitaxel, a structurally complex natural plant product, has demonstrated efficacy in the treatment of a wide variety of human malignancies. This drug shows strong cytotoxicity in KB cell structures and in several of the National Cancer Institute's *in vivo* screens, including the P-388, L-1210, and P-1534 mouse leukemias, the B-16 melanocarcinoma, the CX-1 colon xenograft, the LX-1 lung xenograft, and the MX-1 breast xenograft. Further, studies by McGuire et al. [(1989) *Ann. Int. Med.* 111:273-279] found paclitaxel to be active against drug-refractory ovarian cancer. Positive results were also seen with paclitaxel treatment of patients with other cancers, including melanoma.

Einsig et al. (1988) *Proc. Am. Soc. Clin. Oncol.* 7:249; Holmes (1991) *J. Natl. Cancer Inst.* 83:1797-1805; and Kohn et al. (1994) *J. Natl. Cancer Inst.* 86:18-24.

In addition to various cancers, paclitaxel has been used in treating several other diseases, including malaria and babesiosis. U.S. Patent Nos. 5,356,927 and 5,631,278. Paclitaxel can be used to treat indications characterized by chronic inflammation such as rheumatoid arthritis and auto-immune disease. U.S. Patent No. 5,583,153; and Song et al. (1996) *Arthritis Rheum.* 39:S178. Paclitaxel can impair chronic inflammation by inhibiting the activity of white blood cells involved in the inflammatory response; reducing the production of matrix metalloproteinases that permanently damage tissues; blocking the cancer-like growth of previously normal cells which respond to chronic inflammation by proliferating; and inhibiting the growth of blood vessels which lead to the formation of scar tissue. Paclitaxel is also a potent inhibitor of angiogenesis and other processes involved in the development of chronic inflammation. This activity is due, in part, to paclitaxel's ability to inhibit the transcription factor AP-1. AP-1 is a key regulator of genes involved in the production of (i) matrix metalloproteinases, (ii) cytokines associated with chronic inflammation, and (iii) proteins necessary for cell proliferation. Therefore, paclitaxel inhibits a regulator which plays an important role in chronic inflammation and conditions that are dependent on angiogenesis (new blood vessel formation), including tumor growth. Paclitaxel has shown strong anti-angiogenic activity when tested in the chorioallantoic membrane of the developing chick embryo. The drug is a more potent angiogenesis inhibitor than approved anti-arthritic agents such as methotrexate, penicillamine, and steroids.

Atherosclerosis and restenosis have also been treated with low paclitaxel dosages. U.S. Patent No. 5,616,608. Paclitaxel can alter several aspects of the process leading to restenosis, including inhibition of vascular smooth muscle cell ("VSMC") migration, inhibition of VSMC proliferation, and inhibition of the effects of certain growth factors on these cells. Paclitaxel also inhibits synoviocyte proliferation. Paclitaxel is capable of inhibiting proliferation of synoviocytes *in vitro* and inducing apoptosis (programmed cell death) at concentrations as low as 10^{-7} M, and is cytotoxic to the synoviocytes at slightly higher concentrations of 10^{-6} to 10^{-5} M. Paclitaxel inhibits collagenase production by chondrocytes *in vitro*, but is not toxic to normal chondrocytes. A concentration of 10^{-7} M paclitaxel, for example, reduced collagenase expression by over 50% in cultured

chondrocytes stimulated by tumor necrosis factor and interleukin-1. This inhibition occurs downstream from the transcription factor activity of c-fos and c-jun, apparently by disrupting the normal functioning of the AP-1 molecule, resulting in inhibition of transcription of the collagenase gene. As such, inhibition of collagenase secretion by paclitaxel is not strictly due to interruption of the protein secretory pathway, which is dependent upon microtubule function for the movement of secretory granules. Paclitaxel also appears to act at the level of the genetic response to stimuli directing the cell to produce collagenase.

The drug is also known to be effective in treating a number of other indications. Paclitaxel is useful for treating surgical adhesions and post-surgical hyperplasias. In Alzheimer's disease treatment, paclitaxel has been used to stabilize microtubules destabilized by insufficient tau protein levels. U.S. Patent No. 5,580,898. Paclitaxel is also thought to be effective against polycystic kidney disease (PKD). Sommardahl et al. (1997) *Pediatr. Nephrol.* 11:728-33. Paclitaxel derivatives are also effective in treating psoriasis. EP 747385 and WO 9613494.

Other therapeutic agents have been successfully co-administered with paclitaxel. For example, Vitamin C can be used to increase the efficacy of paclitaxel. Kurbacher et al. (1996) *Cancer Lett.* 103: 183-189. EP 781552 and EP 787716 describe additional compounds that enhance paclitaxel activity. U.S. Patent No. 5,565,478 describes combinational therapy of paclitaxel with signal transduction inhibitors for cancer treatment. In treatment of autoimmune arthritis, paclitaxel has been administered with other antiarthritic drugs, such as an angiogenesis inhibitor. U.S. Patent No. 5,583,153. Anilide derivatives have also been administered to sensitize multidrug-resistant cancer cells to paclitaxel. EP 649410. Paclitaxel can also be administered with antibodies specific to cancerous cells. U.S. Patent No. 5,489,525. In breast cancer treatment, paclitaxel has been administered in combination with estramustine phosphate. Keren-Rosenberg et al. (1997) *Sem. Oncol.* 24 (Suppl. 3):S3-26-29. Paclitaxel and IGF-I (Insulin-like growth factor I) have been used together to treat peripheral neuropathy. U.S. Patent Nos. 5,648,335, 5,569,648 and 5,633,228. Paclitaxel has also been successfully administered along with doxorubicin, cyclophosphamide, and cisplatin. O'Shaughnessy et al. (1995) *Breast Cancer Res. Treat.* 33:27-37. P-glycoprotein blocker SDZ PSC 833, a cyclosporin derivative, has demonstrated a 10-fold increase in oral bioavailability of paclitaxel in mice. Asperen et al.

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