

<p>(51) International Patent Classification <sup>7</sup> : <b>A61K 31/337, 47/48, 47/42</b></p>	<p><b>A1</b></p>	<p>(11) International Publication Number: <b>WO 00/06152</b></p> <p>(43) International Publication Date: 10 February 2000 (10.02.00)</p>
<p>(21) International Application Number: PCT/US99/17179</p> <p>(22) International Filing Date: 29 July 1999 (29.07.99)</p> <p>(30) Priority Data: 60/094,687      30 July 1998 (30.07.98)      US</p> <p>(71) Applicant (for all designated States except US): NOVOPHARM BIOTECH, INC. [CA/CA]; 30 Novopharm Court, Toronto, Ontario M1B 2K9 (CA).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): KADIMA, Tenshuk, A. [CA/CA]; 7 Woodington Bay, Winnipeg, Manitoba R3P 1M6 (CA). KAPLAN, Howard, A. [CA/CA]; 18 Hillhouse Road, Winnipeg, Manitoba R2V 2V9 (CA). TUTTLE, Robert, C. [US/CA]; 782 Allegheny Drive, Winnipeg, Manitoba R3T 5L2 (CA).</p> <p>(74) Agents: WU, Frank et al.; Morrison &amp; Foerster LLP, 755 Page Mill Road, Palo Alto, CA 94304-1018 (US).</p>		<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: PHARMACEUTICALLY ACCEPTABLE COMPOSITION COMPRISING AN AQUEOUS SOLUTION OF PACLITAXEL AND ALBUMIN</p>		
<p>(57) Abstract</p> <p>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.</p>		

*FOR THE PURPOSES OF INFORMATION ONLY*

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

5

CROSS-REFERENCE TO RELATED APPLICATIONS

(Not Applicable)

STATEMENT OF RIGHTS TO INVENTIONS

MADE UNDER FEDERALLY-SPONSORED RESEARCH

10

(Not Applicable)

TECHNICAL FIELD

15

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).

20

BACKGROUND OF THE INVENTION

25

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.

30

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.

# Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

## Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

## LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

## FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

## E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.