PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07K 14/475, A61K 38/18

A1

(11) International Publication Number: **WO 95/22560**

(43) International Publication Date: 24 August 1995 (24.08.95)

(21) International Application Number: PCT/US95/02153

(22) International Filing Date: 21 February 1995 (21.02.95)

(30) Priority Data:
08/200,243 22 February 1994 (22.02.94) US

(71) Applicant: THE SYNTEX-SYNERGEN NEUROSCIENCE JOINT VENTURE [US/US]; 1885 33rd Street, Boulder, CO 80301-2546 (US).

(72) Inventors: DIX, Daniel, B.; 1183 Twin Peaks Circle, Longmont, CO 80503 (US). KOSKY, Andrew, A.; 2958 Alice, Newbury Park, CA 91320 (US). FREUND, Erwin; 801 South County Road 21, Berthoud, CO 80513 (US).

(74) Agents: SWANSON, Barry, J. et al.; Swanson & Bratschun, L.L.C., Suite 200, 8400 East Prentice Avenue, Englewood, CO 80111 (US).

(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).

Published
With international search report.

(54) Title: PHARMACEUTICAL FORMULATIONS OF CNTF

(57) Abstract

Pharmaceutical formulations of ciliary neurotrophic factor (CNTF) are described which are useful for therapeutic treatment of damage to the peripheral nervous system. Formulations of CNTF ideally suited for intrathecal administration are provided.

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.

AT	Austria	**GB**	United Kingdom	**MR**	Mauritania
AU	Australia	**GE**	Georgia	**MW**	Malawi
BB	Barbados	**GN**	Guinea	**NE**	Niger
BE	Belgium	**GR**	Greece	**NL**	Netherlands
BF	Burkina Faso	**HU**	Hungary	**NO**	Norway
BG	Bulgaria	**IE**	Ireland	**NZ**	New Zealand
BJ	Benin	**IT**	Italy	**PL**	Poland
BR	Brazil	**JP**	Japan	**PT**	Portugal
BY	Belarus	**KE**	Kenya	**RO**	Romania
CA	Canada	**KG**	Kyrgystan	**RU**	Russian Federation
CF	Central African Republic	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CG	Congo			**SE**	Sweden
CH	Switzerland	**KR**	Republic of Korea	**SI**	Slovenia
CI	Côte d'Ivoire	**KZ**	Kazakhstan	**SK**	Slovakia
CM	Cameroon	**LI**	Liechtenstein	**SN**	Senegal
CN	China	**LK**	Sri Lanka	**TD**	Chad
CS	Czechoslovakia	**LU**	Luxembourg	**TG**	Togo
CZ	Czech Republic	**LV**	Latvia	**TJ**	Tajikistan
DE	Germany	**MC**	Monaco	**TT**	Trinidad and Tobago
DK	Denmark	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**US**	United States of America
FI	Finland	**ML**	Mali	**UZ**	Uzbekistan
FR	France	**MN**	Mongolia	**VN**	Viet Nam
GA	Gabon				

PHARMACEUTICAL FORMULATIONS OF CNTF

TECHNICAL FIELD OF THE INVENTION

This invention relates to pharmaceutical formulations of ciliary neurotrophic factor suitable for therapeutic treatment of damage to the peripheral nervous system.

BACKGROUND OF THE INVENTION

The peripheral nervous system consists of those nerve cells that extend axonal processes outside the spinal cord and brain. The principle nerve cell types in the peripheral nervous system are primary motor neurons innervating skeletal muscle and controlling movement, autonomic neurons (both sympathetic and parasympathetic) innervating the cardiovascular system and other internal organs and regulating their function, and sensory neurons innervating sensory receptors throughout the body and conveying sensations including pain and proprioception.

Conditions that compromise the survival and proper function of one or more of these types of peripheral nerve cells cause peripheral nerve damage. Such nerve damage may occur from a wide variety of different causes. Nerve damage may occur through physical injury, which causes the degeneration of the axonal processes and/or nerve cell bodies near the site of injury. Nerve damage may also occur because of temporary or permanent cessation of blood flow to parts of the nervous system, as in stroke. Nerve damage may also occur because of intentional or accidental exposure to neurotoxins, such as the cancer and AIDS chemotherapeutic agents cisplatinum and dideoxycytidine (ddC), respectively. Nerve damage may also occur because of chronic metabolic diseases, such as diabetes or renal dysfunction. Nerve damage may also occur because of neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, and

Amyotrophic Lateral Sclerosis (ALS), which result from the degeneration of specific neuronal populations.

Neurotrophic factors are naturally occurring proteins that promote the survival and functional activities of nerve cells. Neurotrophic factors have been found in the target cells to which an innervating nerve cell connects. Such target-derived neurotrophic factors regulate the number of contacts formed between innervating nerve cells and the target cell population, and are necessary for the survival and maintenance of these nerve cells.

Neurotrophic factors are also found in cells that are not innervated. An example of such a neurotrophic factor is CNTF. Human CNTF and the gene encoding human CNTF are described in detail in U. S. patent numbers 4,997,929, and 5,141,856, which are specifically incorporated herein by this reference.

Although the biological role of CNTF has not been conclusively established, CNTF appears to be released upon injury to the nervous system and may limit the extent of injury or neuronal damage. Highly-purified CNTF has been shown to support the survival in cell cultures of chick embryonic parasympathetic, sympathetic, sensory, and motor neurons. There is significant evidence to support that CNTF is a neurotrophic factor for peripheral primary neurons in vivo and in vitro. U. S. patent application serial number 07/735,538 filed July 23, 1991, specifically incorporated herein by reference, shows the surprising effectiveness of systemically administered CNTF to accelerate local recovery at the site of peripheral nerve damage.

The ability of CNTF to protect motor neurons from lesion-induced death may also make it effective in preventing nerve cell degeneration associated with such neurodegenerative diseases as Parkinson's disease, Alzheimer's disease, Amyotrophic Lateral Sclerosis

(ALS), and Spinal Muscular Atrophy (SMA). U.S. patent application serial number 08/015,218 filed February 8, 1993 and U.S. patent application serial number 08/116,440 filed September 3, 1993, both of which are entitled Methods for Treating Amyotrophic Lateral Sclerosis With CNTF, are specifically incorporated herein by reference. These patents present evidence demonstrating the effectiveness of treating amyotrophic lateral sclerosis in humans with CNTF. In addition, Sendtner et al. (1990) Nature 345:440-441, showed that local application of CNTF prevents lesion-induced death of motor neurons in the rat facial brain stem nucleus. Oppenheim et al. (1991) Science 251:1616-1618, showed that CNTF promoted the in vivo survival of chick spinal motor neurons.

A major problem with the delivery of a therapeutically effective amount of CNTF to a patient for treatment or prevention of peripheral nerve damage is the instability of CNTF in solution. CNTF in solution rapidly precipitates when agitated or subjected to thermal incubation. To the extent that any of the protein is denatured, the effective amount of biologically active CNTF is diminished. Protein integrity must therefore be maintained during manufacture and storage as well as during administration. Proteins are particularly prone to degradation at elevated temperatures. Excipients known to physically stabilize proteins in solutions appear to negatively affect the thermal stability of CNTF.

In addition, CNTF is subject to loss from solution by nonspecific adsorption to the surface areas of storage containers and dispensing devices. Such nonspecific binding may occur to a variety of materials including glass and plastics, for example, polyethylene or polypropylene. These materials may be in the form of vials, tubing, syringes, inplantable infusion devices, or any other surface which may come in contact

DOCKET ALARM

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.