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(54) **FORMULATIONS AND METHODS FOR DELAYING ONSET OF CHRONIC NEUROPATHIC PAIN**

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See application file for complete search history.

(56) **References Cited**
U.S. PATENT DOCUMENTS

5,650,428 A 7/1997 Ohmori
5,747,060 A * 5/1998 Sackler A61K 31/165
424/426
5,776,488 A * 7/1998 Mori A61K 9/127
424/450
6,326,020 B1 * 12/2001 Kohane A61K 31/135
424/426
6,803,053 B2 * 10/2004 Papahadjopoulos . A61K 9/0019
424/450
2012/0027844 A1 2/2012 Beckman
2012/0034296 A1 2/2012 Epstein-Barash et al.

FOREIGN PATENT DOCUMENTS

WO 9851290 11/1998
WO WO 98/51290 11/1998
WO 2010117996 10/2010
WO WO 2010/117996 10/2010
WO WO 2010117996 A1 * 10/2010 A61K 31/02

OTHER PUBLICATIONS

Childrens Medical Center Publications Aboul-Fadl, “Antisense oligonucleotides: the state of the art”, *Curr Med Chem.*,12:2193-214 (2005).
Alam, et al., “Design of liposome to improve encapsulation efficiency of gelonin and its effect on immunoreactivity and ribosome inactivating property”, *Mol Cell Biochem.*, 112:97-107 (1992).
Barnet, et al., “Tissue injury from tricyclic antidepressants used as local anesthetics”, *Anesth Analg*, 101(6):1838-43 (2005).
Befort, et al., “Selective up-regulation of the growth arrest DNA damage-inducible gene Gadd45 alpha in sensory and motor neurons after peripheral nerve injury”, *Eur J Neurosci.*, 18(4):911-22 (2003).
Chaim-Matyas, et al., “Encapsulation of the cobra cytotoxin P4 in liposomes”, *Biotechnol Appl Biochem.*, 17(Pt 1): 31-6 (1993).
de Paiva and Dolly, “Light chain of botulinum neurotoxin is active in mammalian motor nerve terminals when delivered via liposomes”, *FEBS Lett.*, 277:171-4 (1990).
Drager, et al., “Prolonged intercostal nerve blockade in sheep using controlled-release of bupivacaine and dexamethasone from polymer microspheres”, *Anesthesiology*, 89(4):969-79.
Freitas and Frezard, “Encapsulation of native crotoxin in liposomes: a safe approach for the production of antivenom and vaccination against *Crotalus durissus terrificus* venom”, *Toxicon.*, 35:91-100 (1997).
Gregoriadis and Allison, “Entrapment of proteins in liposomes prevents allergic reactions in pre-immunised mice”, *FEBS Lett.*, 45:71-4 (1974).
Gregoriadis and Ryman, “Liposomes as carriers of enzymes or drugs: a new approach to the treatment of storage diseases” *Biochem J.*, 124:58P (1971).
Gregoriadis, et al., “Improving the therapeutic efficacy of peptides and proteins: a role for polysialic acids”, *Int J Pharm.* 300:125-30 (2005).
Gregoriadis, “Engineering liposomes for drug delivery: progress and problems”, *Trends Biotechnol.*, 13:527-37 (1995).
Harden, “Chronic neuropathic pain, mechanisms, diagnosis and treatment”, *Neurologist*, 11(2):111-22 (2005).

(Continued)

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(57) **ABSTRACT**

A dosing regimen for formulations that contain a therapeutic dosage of a site 1 sodium channel blocker, where the dosing regimen provides a prolonged nerve block and is in an effective amount to delay the onset of neuropathic pain, such as hyperalgesia and/or allodynia, for at least one week, and preferably longer at the site, and preferably the region (e.g. entire limb), where the nerve block was applied. The site 1 sodium channel blocker is preferably saxitoxin (STX), preferably in combination with a corticosteroid, preferably dexamethasone. In a preferred embodiment, liposomes are included in the formulation as a controlled release system, producing prolonged duration of block without systemic toxicity. As demonstrated by the examples, encapsulating STX in a controlled release system, such as liposomes, preferably also including a corticosteroid, and administering in suitable dosing regimen to achieve a prolonged nerve block without systemic toxicity, delays the onset of hyperalgesia.