



US008362085B2

(12) **United States Patent**
Went et al.

(10) **Patent No.:** **US 8,362,085 B2**
(45) **Date of Patent:** ***Jan. 29, 2013**

(54) **METHOD FOR ADMINISTERING AN NMDA RECEPTOR ANTAGONIST TO A SUBJECT**

(75) Inventors: **Gregory T. Went**, Mill Valley, CA (US);
Timothy J. Fultz, Pleasant Hill, CA (US); **Laurence R. Meyerson**, Las Vegas, NV (US)

(73) Assignee: **Adamas Pharmaceuticals, Inc.**, Emeryville, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/536,525**

(22) Filed: **Jun. 28, 2012**

(65) **Prior Publication Data**

US 2012/0264829 A1 Oct. 18, 2012

Related U.S. Application Data

(60) Continuation of application No. 12/840,132, filed on Jul. 20, 2010, which is a continuation of application No. 12/512,701, filed on Jul. 30, 2009, now Pat. No. 8,168,209, which is a division of application No. 11/285,905, filed on Nov. 22, 2005, now Pat. No. 7,619,007, said application No. 12/512,701 is a continuation-in-part of application No. 11/399,879, filed on Apr. 6, 2006, now Pat. No. 8,058,291, and a continuation-in-part of application No. 11/285,905.

(60) Provisional application No. 60/630,885, filed on Nov. 23, 2004, provisional application No. 60/701,857, filed on Jul. 22, 2005, provisional application No. 60/635,365, filed on Dec. 10, 2004, provisional application No. 60/669,290, filed on Apr. 6, 2005.

(51) **Int. Cl.**

A01N 47/28 (2006.01)
A01N 27/00 (2006.01)
A61K 31/17 (2006.01)
A61K 31/15 (2006.01)
A61K 9/00 (2006.01)

(52) **U.S. Cl.** **514/597**; 514/766; 424/400

(58) **Field of Classification Search** 514/597, 514/766; 424/400

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,152,180 A 10/1964 Haaf
3,391,142 A 7/1968 Mills et al.
3,992,518 A 11/1976 Chien et al.
4,148,896 A 4/1979 Smith et al.
4,273,774 A 6/1981 Scherm
4,284,444 A 8/1981 Bernstein et al.
4,346,112 A 8/1982 Henkel et al.

4,767,628 A 8/1988 Hutchinson
4,769,027 A 9/1988 Baker et al.
4,812,481 A 3/1989 Reischig et al.
4,839,177 A 6/1989 Colombo et al.
4,861,800 A 8/1989 Buyske
4,895,841 A 1/1990 Sugimoto et al.
4,897,268 A 1/1990 Tice et al.
4,904,681 A 2/1990 Cordi et al.
4,948,807 A 8/1990 Rosin et al.
5,057,321 A 10/1991 Edgren et al.
5,061,703 A 10/1991 Bormann et al.
5,061,721 A 10/1991 Cordi et al.
5,086,072 A 2/1992 Trullas et al.
5,162,346 A 11/1992 Lobisch et al.
5,186,938 A 2/1993 Sablotsky et al.
5,190,763 A 3/1993 Edgren et al.
5,192,550 A 3/1993 Edgren et al.
5,221,536 A 6/1993 Edgren et al.
5,334,618 A 8/1994 Lipton
5,358,721 A 10/1994 Guittard et al.
5,382,601 A 1/1995 Numberg et al.
5,395,626 A 3/1995 Kotwal et al.
5,422,120 A 6/1995 Kim
5,422,123 A 6/1995 Conte et al.
5,484,608 A 1/1996 Rudnic et al.
5,502,058 A 3/1996 Mayer et al.
5,521,178 A 5/1996 Nickle et al.
5,601,845 A 2/1997 Buxton et al.
5,614,560 A 3/1997 Lipton et al.
5,648,087 A 7/1997 Ovaert et al.
5,660,848 A 8/1997 Moo-Young
5,726,180 A 3/1998 Kurihara et al.
5,756,115 A 5/1998 Moo-Young et al.
5,891,885 A 4/1999 Caruso
5,912,013 A 6/1999 Rudnic et al.
5,919,826 A 7/1999 Caruso
5,958,919 A 9/1999 Olney et al.
6,046,232 A 4/2000 Kelleher et al.

(Continued)

FOREIGN PATENT DOCUMENTS

AU 2002323873 B2 1/2003
CA 2323805 A1 9/1999

(Continued)

OTHER PUBLICATIONS

Bakchine and Loft, "Memantine Treatment in Patients with Mild to Moderate Alzheimer's Disease: Results of a Randomised, Double-Blind, Placebo-Controlled 6-Month Study" *J Alzheimer's Dis* 11: (2007) 471-479.

(Continued)

Primary Examiner — Sreeni Padmanabhan

Assistant Examiner — Kendra D Carter

(74) *Attorney, Agent, or Firm* — Wilson Sonsini Goodrich & Rosati

(57) **ABSTRACT**

The invention provides methods for administering memantine to a subject. Memantine in an extended release form containing 22.5 to 30 mg memantine or a pharmaceutically acceptable salt is administered to a patient suffering from a neurological condition, such as Alzheimer's disease, Parkinson's disease or dementia. The extended release form achieves particular pharmacokinetic criteria such as change in plasma concentration of memantine over time and ratio of maximum memantine plasma concentration to mean memantine plasma concentration.

U.S. PATENT DOCUMENTS

6,057,364 A 5/2000 Jasy et al.
 6,066,652 A 5/2000 Zenner et al.
 6,114,392 A 9/2000 Gilad et al.
 6,183,770 B1 2/2001 Muchin et al.
 6,187,338 B1 2/2001 Caruso et al.
 6,194,000 B1 2/2001 Smith et al.
 6,217,905 B1 4/2001 Edgren et al.
 6,258,827 B1 7/2001 Chenard et al.
 6,284,276 B1 9/2001 Rudnic et al.
 6,384,083 B1 5/2002 Ludwig et al.
 6,392,104 B1 5/2002 Ishii et al.
 6,444,702 B1 9/2002 Wang et al.
 6,479,553 B1 11/2002 McCarthy
 6,491,949 B2 12/2002 Faour et al.
 6,500,454 B1 12/2002 Percel et al.
 6,620,845 B2 9/2003 Wang et al.
 6,635,268 B2 10/2003 Peery et al.
 6,648,083 B2 11/2003 Evans et al.
 6,662,845 B1 12/2003 Palmer
 6,715,485 B1 4/2004 Djupesland
 6,717,012 B2 4/2004 Wang et al.
 6,743,211 B1 6/2004 Prausnitz et al.
 6,746,689 B2 6/2004 Fischer et al.
 6,764,697 B1 7/2004 Jao et al.
 6,770,295 B1 8/2004 Kreilgard et al.
 6,797,283 B1 9/2004 Edgren et al.
 6,852,889 B2 2/2005 Wang et al.
 6,913,768 B2 7/2005 Couch et al.
 6,919,373 B1 7/2005 Lam et al.
 6,923,800 B2 8/2005 Chen et al.
 6,929,803 B2 8/2005 Wong et al.
 6,930,128 B2 8/2005 D'Amato et al.
 6,939,556 B2 9/2005 Lautenbach
 6,945,952 B2 9/2005 Kwon
 7,619,007 B2 11/2009 Went et al.
 2002/0035105 A1 3/2002 Caruso
 2002/0071863 A1 6/2002 Dong et al.
 2003/0190354 A1 10/2003 Sela
 2003/0198683 A1 10/2003 Li et al.
 2003/0203055 A1 10/2003 Rao et al.
 2004/0087658 A1 5/2004 Moebius
 2004/0102525 A1 5/2004 Kozachuk
 2004/0122090 A1 6/2004 Lipon
 2004/0224020 A1 11/2004 Schoenhard
 2004/0254251 A1 12/2004 Firestone et al.
 2005/0020319 A1 1/2005 Kim et al.
 2005/0031651 A1 2/2005 Gervais et al.
 2005/0065219 A1 3/2005 Lipton et al.
 2005/0124701 A1 6/2005 Went et al.
 2005/0153953 A1 7/2005 Trippodi-Murphy et al.
 2005/0191349 A1 9/2005 Boehm et al.
 2005/0203191 A1 9/2005 McDonald et al.
 2005/0208132 A1 9/2005 Sathyan et al.
 2005/0209218 A1 9/2005 Meyerson
 2005/0232990 A1 10/2005 Boehm et al.
 2005/0245460 A1 11/2005 Meyerson
 2005/0245617 A1 11/2005 Meyerson et al.
 2005/0267176 A1 12/2005 Barberich
 2006/0002999 A1 1/2006 Yang et al.
 2006/0020042 A1 1/2006 McDonald et al.
 2006/0051416 A1 3/2006 Rastogi et al.
 2006/0052370 A1 3/2006 Meyerson
 2006/0062851 A1 3/2006 Vergez et al.
 2006/0063810 A1 3/2006 Vergez et al.
 2006/0079578 A1 4/2006 Laurin et al.
 2006/0142398 A1 6/2006 Went et al.
 2006/0159763 A1 7/2006 Meyer et al.
 2006/0160852 A1 7/2006 Kimura et al.
 2006/0189694 A1 8/2006 Went et al.
 2006/0198884 A1 9/2006 Yang et al.
 2006/0240043 A1 10/2006 Meyerson
 2006/0246003 A1 11/2006 Kimura et al.
 2006/0252788 A1 11/2006 Went et al.
 2007/0065512 A1 3/2007 Dedhiya et al.
 2008/0260825 A1 10/2008 Quik et al.
 2008/0279819 A1 11/2008 Went et al.

2010/0137448 A1 6/2010 Lipton et al.
 2010/0260838 A1 10/2010 Went et al.
 2010/0266684 A1 10/2010 Went et al.
 2010/0311697 A1 12/2010 Went et al.
 2011/0059169 A1 3/2011 Went et al.

FOREIGN PATENT DOCUMENTS

EP 0350080 1/1990
 EP 0392059 A1 10/1990
 EP 0451484 A1 10/1991
 EP 0452484 B2 10/1991
 EP 0488959 A2 11/1991
 EP 0488959 A3 8/1992
 EP 0502642 A1 9/1992
 EP 0524968 2/1993
 EP 0731359 9/1996
 EP 0870757 A2 10/1998
 EP 0927711 A1 7/1999
 EP 0870757 A3 6/2000
 EP 1559418 8/2005
 EP 1600156 11/2005
 EP 1509232 B1 11/2008
 FR 2219159 9/1974
 GB 1173492 A 12/1969
 JP 58-4718 1/1983
 JP 10203966 A 8/1998
 WO 89/09051 A1 10/1989
 WO 91/06291 A1 5/1991
 WO 91/14445 A1 10/1991
 WO 92-17168 10/1992
 WO 94/05275 A1 3/1994
 WO 94/06428 A1 3/1994
 WO 95/13796 A1 5/1995
 WO 97-02273 1/1997
 WO 97/14415 A1 4/1997
 WO 98/07447 2/1998
 WO 98-07447 2/1998
 WO 98/18457 A1 3/1998
 WO 98-15275 4/1998
 WO 98/27961 A2 7/1998
 WO 98/27961 A3 9/1998
 WO 98-50044 11/1998
 WO 00-00197 1/2000
 WO 00-03716 1/2000
 WO 00/18378 A1 4/2000
 WO 00-29023 5/2000
 WO 00-54810 9/2000
 WO 00/56301 A2 9/2000
 WO 00/56301 A3 12/2000
 WO 01-08682 2/2001
 WO 01/19901 A2 3/2001
 WO 01/32115 A1 5/2001
 WO 01/32148 A1 5/2001
 WO 01/46291 A1 6/2001
 WO 01/62706 A1 8/2001
 WO 01/19901 A3 9/2001
 WO 01-91753 12/2001
 WO 03-094812 11/2003
 WO 03/101458 A1 12/2003
 WO 2004/012700 A2 2/2004
 WO 2004/012700 A3 4/2004
 WO 2004/037234 A2 5/2004
 WO 2004-056335 7/2004
 WO 2004/056335 A2 7/2004
 WO 2004/037234 A3 8/2004
 WO 2004-087116 10/2004
 WO 2004/087116 A2 10/2004
 WO 2004/056335 A3 11/2004
 WO 2004/087116 A3 12/2004
 WO 2004/112768 A1 12/2004
 WO 2005-058420 6/2005
 WO 2005/065645 A2 7/2005
 WO 2005/072705 A1 8/2005
 WO 2005-079773 9/2005
 WO 2005/079773 A2 9/2005
 WO 2005-079779 9/2005
 WO 2005-084655 9/2005

WO	WO 2005/092009	A2	10/2005
WO	WO 2006/009769	A1	1/2006
WO	WO 2005/092009	A3	2/2006
WO	WO 2006/070781	A1	7/2006
WO	WO 2006/089494	A1	8/2006
WO	WO 2006/138227	A1	12/2006

OTHER PUBLICATIONS

Carlton, S.M., Hargett, G.L., Treatment with the NMDA antagonist memantine attenuates nociceptive responses to mechanical stimulation in neuropathic rats. *Neurosci. Lett.* 198, 115-118. (1995).

Eisenberg, E., LaCross, S., Strassman, M. The clinically tested N-methyl-D-aspartate receptor antagonist memantine blocks and reverses thermal hyperalgesia in a rat model of painful mononeuropathy. *Neurosci. Lett.* 187, 17-20 (1995).

Johannsen P. "Long-Term Cholinesterase Inhibitor Treatment of Alzheimer's Disease" *CNS Drugs* (2004) 18(12):757-68.

Keilhoff et al., Memantine prevents quionlinic acid-induced hippocampal damage. *Eur. J. Pharmacol.* 219:451-454, (1992).

Kornhuber and Quack. "Cerebrospinal fluid and serum concentrations of the N-methyl-D-aspartate (NMDA) receptor antagonist memantine in man." *Neurosci. Letters*, 195:137-139 (1995).

Lanctot et al., "Efficacy and safety of cholinesterase inhibitors in Alzheimer's disease: a meta-analysis" *Canadian Medical Association Journal* (2003) 169:557-64.

Lipton et al., Excitatory Amino Acids as a Final Common Pathway for Neurologic Disorders, *N. Engl. J. Med.* 330(9) :613-622 (1994).

Neugebauer, V., Kornhuber, J., Lu cke, T., Schaible, H.G., The clinically available NMDA receptor antagonist memantine is antinociceptive on rat spinal neurones. *Neuroreport* 4, 1259-1262. (1993).

Parsons CG, Gruner R, Rozental J, Millar J, Lodge D. Patch clamp studies on the kinetics and selectivity of N-methyl-D-aspartate receptor antagonism by memantine, (1-amino-3,5-dimethyladarnantan). *Neuropharmacology* ;32:1337-1350 (1993).

Parsons, at al., (2001) NMDA receptors as targets for drugs in neuropathic pain. *Eur. J. Pharmacology*, 429, 71-78 (2001).

Rogers et al., A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease, *Neurology* (1998) 50:136-45.

Sobolevsky AI, Koshelev SG, Khodorov BI. Interaction with agonist-unbound NMDA-receptor channels in acutely isolated rat hippocampal neurons. *J Physiol* (1998) 512(Pt 1).47-60.

Winblad et al., "A 1-year, randomized, placebo-controlled study of donepezil in patients with mild to moderate AD," *Neurology* (2001) 57 :489-95.

EP 1874282 Patentee's Written Submissions Under Rule 116 EPC dated Sep. 7, 2012.

Reichman, "Current pharmacologic options for patients with Alzheimer's disease," *Annals of General Hospital Psychiatry*, vol. 2, pp. 1-14 (2003).

Wilcock G. Mobius HJ, Stoffler A; MNIM 500 group. A double-blind, placebo-controlled multicentre study of memantine in mild to moderate vascular dementia (MMM500). *Int Clin Psychopharmacol.* Nov. 2002;17(6):297-305.

Anand et al., "Dissolution Testing: An FDA Perspective," *AAPS Workshop, Physical Pharmacy and Biopharmaceutics*, May 13, 2009, 1-32.

Bashki et al., "Fatigue in Multiple Sclerosis and Its Relationship to Depression and Neurologic Disability," *Mult Scler* 6:181-5 (2000).

Ing et al., "Toxic Effects of Amantadine in Patients with Renal Failure," *CMA Journal*, Mar. 1979, vol. 120. pp. 695-697.

Mann, "The Medical Management of Depression," *New England Journal of Medicine*, 353 :1819-34 (2005).

Siebert et al., "Depression in Multiple Sclerosis; a review," *J Neurol Neurosurg Psychiatry* 76:469-75 (2005).

Almeida et al., "Evidence for the involvement of L-arginine-nitric oxide-cyclic guanosine monophosphate pathway in the antidepressant-like effect of memantine in mice" *Behavioural Brain Research*,

Bonnet, "Involvement of non-dopaminergic pathways in Parkinson's disease: Pathophysiology and therapeutic implications" *CNS Drugs*, vol. 13, No. 5, May 2000, pp. 351-364, XP009068859 ISSN: 1172-7047.

Delagarza et al., "Pharmacologic Treatment of Alzheimer's Disease: an Update," *Am. Fam. Phys.* vol. 68, No. 7, 2003, pp. 136-572.

Dong et al., "Acetylcholinesterase inhibitors ameliorate behavioral deficits in the Tg2576 mouse model of Alzheimer's disease," *Psychopharmacology* vol. 181, No. 1, 2005, pp. 145-152.

Engber, et al., "NMDA receptor blockade reverses motor response alterations induced by levodopa" *Neuroreport*, vol. 5, No. 18, 1994, pp. 2586-2588, XP009068863 ISSN: 0959-4965.

Franz et al., "Percutaneous Absorption on the Relevance of In Vitro Data," *J. Invest. Derm.* vol. 64, 1975, pp. 194-195.

Fredriksson et al., "Co-administration of memantine and amantadine with sub/suprathreshold doses of L-Dopa restores motor behaviour of MPTP-treated mice" *Journal of Neural Transmission*, vol. 108, No. 2, 2001, pp. 167-187, XP002389118 ISSN: 0300-9564.

Greenamyre et al., "Antiparkinsonian effects of remacemide hydrochloride, a glutamate antagonist, in rodent and primate models of Parkinson's disease" *Annals of Neurology*, vol. 35, No. 6, 1994, pp. 655-661, XP009068858 ISSN: 0364-5134.

Jost, "Therapy in the early stage of idiopathic Parkinson's disease" *Nervenheilkunde* 2005 Germany, vol. 24, No. 1, 2005, pp. 24-28, XP009046893 ISSN: 0722-1541 with English Summary.

Koch et al., "Anodic Chemistry of Adamantyl Compounds. Some Scissible Carbon, Halogen, Hydrogen, and Oxygen Substituents" *Journal of the American Chemical Society*, vol. 95, No. 26, Dec. 26, 1973, pp. 8631-8637, XP002170382 American Chemical Society, Washington, DC., US ISSN: 0002-7863.

Kotani et al., "A New Combined Oxidizing Reagent System, Hexakisacetoneiron(III) periodate: Oxidation of Paraffin Hydrocarbons" *Chemical and Pharmaceutical Bulletin*, vol. 33, No. 11, Nov. 1985, pp. 4680-4684, XP002170380 Tokyo JP.

Mastrosimone et al., "Personal Experience With a Combination of Drugs in Subjects With Dopa Resistant Parkinson's Disease" *Journal of Medicine*, Karger, Basel, CH, vol. 11, No. 5/6, 1980, pp. 377-383, XP009038480 ISSN: 0025-7850.

Mella et al., "Oxidative-Functionalization of Adamantane and Some of Its Derivatives in Solution" *Journal of Organic Chemistry*, vol. 61, No. 4, 1996, pp. 1413-1422, XP002170381 American Chemical Society, Easton., US ISSN: 0022-3263.

Merims D et al., "Riluzole for le vodopa-induced dyskinesias advanced Parkinson's disease" *Lancet The, Lancet Limited*, London, GB, vol. 153, No. 9166.22 May 1999, pp. 1764-1765, XP004826824 ISSN: 0140-6736.

Metman L Verhagen et al., "Amantadine as treatment for dyskinesias and motor fluctuations in Parkinson's disease" *Neurology*, vol. 50, No. 5, May 1998, pp. 1323-1326, XP009068857 ISSN: 0028-3878.

Metman et al., "A Trial of Dextromethorphan in Parkinsonian Patients With Motor Response Complications" *Movement Disorders*, Raven Press, New York., NY, US, vol. 13, No. 3, May 1998, pp. 414-417, XP009066519 ISSN 0885-3185.

Papa et al., "Levodopa-Induced Dyskinesia Improved by a Glutamate Antagonist in Parkinsonian Monkeys" *Annals of Neurology*, Boston, US, vol. 39, May 1996, pp. 574-578, XP002090027 ISSN: 0364-5134.

Parsons et al.: 'Glutamate in CNS disorders as a target for drug development: an update', XP002908604 Retrieved from STN Database accession No. 131:13198 & Drug News Perspect. vol. 11, No. 9, 1998, pp. 523-569.

Rogoz et al., "Synergistic effect of uncompetitive NMDA receptor antagonists and antidepressant drugs in the forced swimming test in rats" *Neuropharmacology*, Pergamon Press, Oxford, GB, vol. 42, No. 8, Jun. 2002, pp. 1024-1030, XP002288820 ISSN: 0028-3908.

Shefrin, "Therapeutic advances in idiopathic Parkinsonism" *Expert Opinion on Investigational Drugs* 1999 United Kingdom, vol. 8, No. 10, 1999, pp. 1565-1588, XP002389119 ISSN: 1354-3784.

Shuto Satoshi et al., "(1S,2R)-1-Phenyl-2-Ä(S)-1-aminopropylÜ-N, N-diethylcyclopropane-carbox amide)PPDC) a New Class of

- cology, The Japanese Pharmacological Society, Kyoto, JP, vol. 85, No. 3, Mar. 2001, pp. 207-213, XP008021088 ISSN: 0021-5198.
- Snijdelaar et al., "Effects of Perioperative Oral Amantadine on Post-operative Pain and Morphine Consumption in Patients after Radical Prostatectomy: Results of a Preliminary Study" *Anesthesiology* 2004 United States, vol. 100, No. 1, Jan. 2004, pp. 134-141, XP009057749 ISSN: 0003-3022.
- Spieker et al., "The NMDA antagonist budipine can alleviate levodopa-induced motor fluctuations." *Movement Disorders: Official Journal of the Movement Disorder Society*, May 1999, vol. 14, No. 3, May 1999, pp. 517-519, XP009068946 ISSN: 0885-3185.
- Sviridov et al., 'C-hydroxyalkylation of N-adamantylanilines with hexafluoroacetone and methyl trifluoropyruvate', XP002958124 Database CAPLUS [Online] Retrieved from STN Database accession No. 1990:197720 & Izv. Akad. NAUK SSSR, Ser. Khim. No. 10, 1989, pp. 2348-2350.
- Urbanska et al., "Antiparkinsonian drugs memantine and trihexylphenidyl potentiate the anticonvulsant activity of valproate against maximal electroshock-induced seizures" *Neuropharmacology*, vol. 31, No. 10, 1992, pp. 1021-1026, XP002332724.
- Van Dam et al. "Symptomatic effect of donepezil, rivastigmine, galatamine and memantine on cognitive deficits in the APP23 model," *Psychopharmacology* vol. 180, No. 1, 2005, pp. 177-190.
- Weiler et al., "The use of Propranolol in Alzheimer's Disease Patients with Disruptive Behavior" *Current Therapeutic Research*, vol. 42, No. 2, Aug. 1987, pp. 364-374, XP001027133.
- Wessell, et al., "NR2B selective NMDA receptor antagonist CP-101,606 prevents levodopa-induced motor response alterations in hemi-parkinsonian rats" *Neuropharmacology*, vol. 47, No. 2, Aug. 2004, pp. 184-194, XP002389117 ISSN: 0028-3908.
- Zarate et al. "A double-blind, placebo-controlled study of memantine in the treatment of major depression" *American Journal of Psychiatry*, vol. 163, No. 1, Jan. 2006, pp. 153-155, XP009087802 ISSN:0002-953X.
- PCT/US2005/042780 International Search Report dated Sep. 8, 2006.
- EP 05852057 (EP 1827385 A) Third Party Submission Undet Art. 115 EPC dated May 25, 2012.
- Maier et al., "Efficacy of the NMDA-receptor antagonist memantine in patients with chronic phantom limb pain—results of a randomized double-blinded, placebo-controlled trial," *Pain*, 103, pp. 277-283 (2003).
- Namenda label, NDA 21-487, pp: 1-20. Forest Pharmaceuticals, Inc. (2007).
- Pharmaceutical Dosage Forms: Tablets, Second Edition, Revised and Expanded, published by Marcel Dekker, Inc., edited by Lieberman, Lachman, and Schwartz. (1990) pp. 462-472.
- Remington, *The Science and Practice of Pharmacy*, 21ST Ed., pp. 944-945 (2006).
- Swerdlow et al., "The Effects of Memantine on Prepulse Inhibition," *Neuropsychopharmacology*, 34, pp. 1854-1864 (2009).
- Vale et al., "Amantadine in Depression," *Lancet*, 11,437 (1971).
- International search report dated Apr. 5, 2002 for PCT Application No. US2001/48516.
- International search report dated May 8, 2006 for PCT Application No. US2005/42424.
- "Pharmazeutische Technologie" 5th Ed. w/ English Translation (1997).
- "Pharmazeutische Technologie" 9th Ed. w/ English Translation (2000).
- Annex A (Letter from Mint Levin dated Jan. 27, 2009) from Oral Proceedings request of May 30, 2012.
- Annex B (Additional data) from Oral Proceedings request of May 30, 2012.
- EP1874282 (Appl. No. 06749777.6) Opposition Against Patent dated Jun. 10, 2011.
- EP1874282 (Appl. No. 06749777.6) Oral Proceedings Request dated May 30, 2012.
- EP1874282 (Appl. No. 06749777.6) Granted Patent Claims—granted Sep. 15, 2010.
- Ambrozi, et al. Treatment of Impaired Cerebral Function in Psychogeriatric Patients with Memantine—Results of a Phase II Double-Blind Study. *Pharmacopsychiat.* 1988;21(3):144-6.
- Avery's Drug Treatment; Principles and Practice of Clinical Pharmacology and Therapeutics, 3rd Edition, 1987, edited by Trevor M. Speight, Chapter VIII, pp. 255-282.
- Barth et al. Combination therapy with MK-801 and alpha-phenyl-tert-butyl-nitron enhances protection against ischemic neuronal damage in organotypic hippocampal slice cultures. *Exp Neurol.* 1996;141(2):330-6.
- Bayerl, et al. Klinische Vergleichsstudie der Antispastika Memantin und Baclofen. (Clinical Comparative Study of the Antispastic Compounds Memantine and Baclofen). *Therapiewoche* 1988;35: 5440-5444, (with English abstract).
- Beers, M.H. and Berkow, R. Editors-in-chief, *The Merck Manual of Diagnosis and Therapy*, 17th Edition, pp. 1525-1544, 1999.
- Bentue-Ferrer, et al. Medication in Alzheimer's disease, *Rev. Geriatr.* 26(6):511-522 (2001), (in French with English summary).
- Berman, et al. Antidepressant effects of ketamine in depressed patients. *Biol. Psychiatry.* 2000;47:351-354.
- Bhat, et al. Localization of the N-methyl-D-aspartate R1 receptor subunit in specific anterior pituitary hormone cell types of the female rat. *Neuroendocrinol.* 1995;62(2):178-186.
- Bliss, et al. A synaptic model of memory: long-term potentiation in the hippocampus. *Nature.* 1993;361:31-39.
- Bormann, J. Memantine is a potent blocker of N-methyl-D-aspartate (NMDA) receptor channels. *Eur. J. Pharmacol.* 1989;166:591-592.
- Braga, et al. Making crystals from crystals: a green route to crystal engineering and polymorphism, *Chemical Communications* pp. 3635-3645 (2005).
- Bredt, et al. Localization of nitric oxide synthase indicating a neural role for nitric oxide. *Nature.* 1990;347:768-770.
- Budziszewska, et al. Antidepressant drugs inhibit glucocorticoid receptor-mediated gene transcription—a possible mechanism, *Br J Pharmacol.* Jul. 2000;130(6):1385-93.
- Bull, Drug review—Memantine, *Drugs in Context* 2005, I(I):1-40.
- Cacabelos, et al. Pharmacological treatment of Alzheimer disease: from psychotropic drugs and cholinesterase inhibitors to pharmacogenomics. *Drugs Today.* 2000; 36(7):415-499.
- Calabrese, et al. A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. Lamictal 602 Study Group. *J. Clin. Psychiatry.* 1993;60:79-88.
- Camps, et al. Cholinergic drugs in pharmacotherapy of Alzheimer's disease. *Mini Rev Med Chem.* Feb. 2002;2(1):11-25.
- Chamulitrat, et al. Nitric oxide formation during light-induced decomposition of phenyl N-tert-butyl nitron. *J. Biol. Chem.* 1993; 268(16):11520-11527.
- Chen, et al. Mechanism of memantine block of NMDA-activated channels in rat retinal ganglion cells: uncompetitive antagonism. *J. Physiol.* 1997; 499(1):27-46.
- Chen, et al. Neuroprotective concentrations of the N-methyl-D-aspartate open-channel blocker memantine are effective without cytoplasmic vacuolation following post-ischemic administration and do not block maze learning or long-term potentiation. *Neurosci.* 1998; 86(4):1121-1132.
- Chen, et al. Open-channel block of N-methyl-D-aspartate (NMDA) responses by memantine: therapeutic advantage against NMDA receptor-mediated neurotoxicity. *J. Neurosci.* 1992;12(11):4427-4436.
- Choi, DW. Glutamate neurotoxicity and diseases of the nervous system. *Neuron.* 1988;1:623-634.
- Chung, et al. Clinical pharmacokinetics of doxazosin in a controlled-release gastrointestinal therapeutic system (GITS) formulation; *Br J Clin Pharmacol* 1999, 48:678-87.
- Cohan, et al. Electrically and chemically mediated increases in intracellular calcium in neuronal growth cones. *J. Neurosci.* 1987;7(11):3588-3599.
- Connor, et al. Depolarization- and transmitter-induced changes in intracellular Ca²⁺ of rat cerebellar granule cells in explant cultures. *J. Neurosci.* 1987;7(5):1384-1400.
- Connor, et al. Sustained dendritic gradients of Ca²⁺ induced by

- Cummings, J. L. Depression and Parkinson's Disease: A Review. *The American Journal of Psychiatry*. 1992;149(4): 443-454.
- Cutler, RG. Human longevity and aging: possible role of reactive oxygen species. *Ann. New York Acad. Sci.* 1991;621:1-28.
- Danzysz, et al. Aminoadamantanes as NMDA receptor antagonists and antiparkinsonian agents—preclinical studies. *Neurosci. Biobehav. Rev.* 1997;21(4):455-468.
- Danzysz, et al. Memantine provides neuronprotection in animal models at therapeutically relevant doses. Abstracts from the 8th International Conference on Alzheimer's Disease and Related Disorders. Stockholm, Sweden. Jul. 20-25, 2002, No. 297.
- Ditzler, K. Efficacy and Tolerability of Memantine in Patients with Dementia Syndrome, *Arzneim.-Forsch./Drug Res.* 41 (II), Nr. 8, 773-780 (1991), Bad Krozingen, Germany.
- Dooley, et al. Donepezil: A review of its use in Alzheimer's Disease, *Drugs and Aging* 16(3):199-226 (2000).
- Dreyer, et al. HIV-1 coat protein neurotoxicity prevented by calcium channel antagonists. *Science*. 1990;248:364-367.
- Edamatsu, et al. The spin-trap N-tert-alpha-phenyl-butyl nitron prolongs the life span of the senescence accelerated mouse. *Biochem. Biophys. Res. Commun.* 1995;211(3):847-849.
- Edwards, K.R. New Studies on the Pharmacologic Treatment of Painful Neuropathies, Especially in Painful Diabetic Polyneuropathy, 52nd Annual Meeting of the American Academy of Neurology, Apr. 29-May 6, 2000, San Diego, CA, <http://www.medscape.com/viewarticle/420246>.
- Eisenberg, et al. The effects of the clinically tested NMDA receptor antagonist memantine on carrageenan-induced thermal hyperalgesia in rats. *Eur. J. Pharmacol.* 1994;255(1-3):123-9.
- Eisenberg, et al. The NMDA antagonist Memantine blocks pain behavior in a rat model of formalin-induced facial pain. *Pain*. 1993;54(3):301-7.
- European search report dated Oct. 15, 2007 for Application No. 07000173.0.
- European Search Report for EP 01 99 0191, mailed May 26, 2004.
- FDA Medical Review for Namenda, RTM. NDA 21-487, Oct. 2, 2003, pp. 1-113.
- Feldman, et al. A 24-Week, randomized double-blind study of donepezil in moderate to severe Alzheimer's Disease, *Neurology* 57:613-20 (2001).
- Fischer, et al. The effect of intravenous administration of memantine in parkinsonian patients (author's translation). *Arzneimittelforschung*. 1977;27(7):1487-1489 (in German with English).
- Fleischhacker, et al. Memantine in the treatment of senile dementia of the Alzheimer type. *Prog. Prog Neuropsychopharmacol Biol Psychiatry*. 1986;10(1):87-93.
- Forstl, H. Symptomatic therapy of Alzheimer dementia, *Wien Med Wochenschr.* 2002;152(3-4):77-80 (in German with English translation).
- Foster, et al. Neurobiology. Taking apart NMDA receptors. *Nature*. 1987;329(6138):395-6.
- Fox, et al. Memantine combined with an acetyl cholinesterase inhibitor—hope for the future? *Neuropsychiatr Dis Treat.* Jun. 2006;2(2):121-5.
- Fuchsbeher, et al. Starting Alzheimer therapy in early stages whenever possible. Activities of daily living remain intact longer, *MMW Fortschr Med.*, 144(20):36-9 (2002); (in German with English summary).
- Galli, et al. Acetylcholinesterase inhibition and protection by dizocilpine (MK-801) enantiomers. *J Pharm Pharmacol*, Jan. 1996;48(1):71-6.
- Garthwaite, et al. Endothelium-derived relaxing factor release on activation of NMDA receptors suggests role as intercellular messenger in the brain. *Nature*, 1988;336(6197):385-8.
- Gauthier, et al. Effects of memantine on behavioural symptoms in Alzheimer's disease patients: an analysis of the Neuropsychiatric Inventory (NPI) data of two randomised, controlled studies. *Int J Geriatr Psychiatry*, May 2005;20(5):459-64.
- Gauthier, et al. Functional, Cognitive, and Behavioral Effects of Donepezil in Patients with Moderate Alzheimer's Disease, *Current Medical Research and Opinion*® 18(6): 347-54 (2002).
- Gortelmeyer, et al., Memantine in the Treatment of Mild to Moderate Dementia Syndrome, *Arzneim.-Forsch./ Drug Res.* 42 (II), Nr. 7, 904-913 (1992), Frankfurt, Germany.
- Graham, et al. Plasma homocysteine as a risk factor for vascular disease. The European Concerted Action Project. *JAMA*. 1997 277(22):1775-1781.
- Greenberg, et al. Treatment of Major Depression and Parkinson's Disease with Combined Phenelzine and Amantadine. *Am. J. Psychiatry*. 1985;142(2):273-274.
- Greene, T.W. Protective Groups in Organic Synthesis. John Wiley & Sons; pp. 70-71 (1981).
- Grossmann, et al. Memantine and neurogenic bladder disorders in spastic clinical pictures, *Arzneim.-Forsch./Drug Res.* 1982, 32(II)(10):1273-6. (in German with English Summary).
- Grynkiwicz, et al. A new generation of Ca²⁺ indicators with greatly improved fluorescence properties. *J. Biol. Chem.* 1985;260(6):3440-3450.
- Gupta, et al. Novel effects of memantine in antagonizing acute aldicarb toxicity: Mechanistic and applied considerations. *Drug development research*. 1991; 24:329-341.
- Gupta, et al. Prevention and antagonism of acute carbofuran intoxication by memantine and atropine, *J Toxicol Environ Health*, 1989;28(1):111-22.
- Hahn, et al. Central mammalian neurons normally resistant to glutamate toxicity are made sensitive by elevated extracellular Ca²⁺: toxicity is blocked by the N-methyl-D-aspartate antagonist MK-801. *Proc. Natl. Acad. Sci. USA*. 1998;85(17):6556-60.
- Hartmann, et al. Tolerability of memantine in combination with cholinesterase inhibitors in Alzheimers disease and vascular dementia. Abstracts from the 8th International Conference on Alzheimer's Disease and Related Disorders. Stockholm, Sweden. Jul. 20-25, 2002, No. 317.
- Hartmann, et al. Tolerability of memantine in combination with cholinesterase inhibitors in dementia therapy. *Int. Clin. Psychopharmacol*, 2003, 18(2):81-85.
- Helmuth, L. New Alzheimer's treatments that may ease the mind. *Science*. Aug. 23, 2002;297(5585):1260-2.
- Ho, et al. Memantine: A New Treatment Option for Patients with Moderate-to-Severe Alzheimer's Disease, *P&T*, vol. 29 No. 3, Mar. 2004.
- Hoffmann, et al. Eight-year prescription trends of memantine and cholinesterase inhibitors among persons 65 years and older in Germany. *Int Clin Psychopharmacol*. Jan. 2010;25(1):29-36.
- Ihl, R. Dementing disorders. What benefits do the new anti-dementia drugs have? *MMW Fortschr Med.* May 6, 2002;Suppl 2:24-6, 28-9 (in German with English translation).
- International search report dated Apr. 5, 2002 for PCT Application No. US2001/48516.
- International Search Report for PCT/US2006/013506, mailed Jan. 12, 2007, Feb. 23, 2007 Corrected.
- Jain, et al. Evaluation of memantine for neuroprotection in dementia, *Exp. Opin. Invest. Drugs*, 2000, 9(6):1-10.
- Jain, et al. Polymorphism in Pharmacy, *Indian Drugs* 23(6):3 15-29 (1986).
- Jain, K.K. Evaluation of ineniantine for neuroprotection in dementia. *Expert Opin. Investig Drugs*. Jun. 2000; 9(6):1397-406.
- Janzen, et al. Stabilities of hydroxyl radical spin adducts of PBN-type spin traps. *Free Rad. Biol. Med.* 1992;12(2):169-73.
- Johnson, et al. Neuropharmacology of phencyclidine: basic mechanisms and therapeutic potential. *Annu. Rev. Pharmacol. Toxicol.* 1990; 30:707-750.
- Karcz-Kubicha, et al. Anxiolytic activity of glycine-B antagonists and partial agonists—no relation to intrinsic activity in the patch clamp. *Neuropharmacol.* 1997;36(10):1355-67.
- Keilhoff, et al. Memantine prevents quinolinic acid-induced hippocampal damage. *Eur. J. Pharmacol.* 1992;219:451-454.
- Klockgether, et al. Excitatory amino acids and the basal ganglia: implications for the therapy of Parkinson's disease. *Trends Neurosci.* 1989;12(8):285-286.
- Klockgether, et al. NMDA antagonists potentiate antiparkinsonian

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.