

US008772306B

(12) United States Patent Eller

(10) Patent No.: US 8,772,306 B1 (45) Date of Patent: *Jul. 8, 2014

(54) METHOD OF ADMINISTRATION OF GAMMA HYDROXYBUTYRATE WITH MONOCARBOXYLATE TRANSPORTERS

- (71) Applicant: Jazz Pharmaceuticals, Inc., Palo Alto, CA (US)
- (72) Inventor: Mark Eller, Redwood City, CA (US)
- (73) Assignee: Jazz Pharmaceuticals, Inc., Palo Alto, 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.: 13/872,997
- (22) Filed: Apr. 29, 2013

Related U.S. Application Data

- (63) Continuation of application No. 13/837,714, filed on Mar. 15, 2013.
- (60) Provisional application No. 61/771,557, filed on Mar. 1, 2013, provisional application No. 61/777,873, filed on Mar. 12, 2013.
- (51) Int. Cl.
 A61K 31/505 (2006.01)
 A61K 31/33 (2006.01)
 A61K 31/55 (2006.01)
 (52) U.S. Cl.
- USPC 514/275; 514/183; 514/214.03 (58) Field of Classification Search

(56) References Cited

U.S. PATENT DOCUMENTS

3.325.361	А	6/1967	Meunier
3,385,886		5/1968	Nicholson et al.
4,155,929		5/1979	Chignac et al.
4.393.236		7/1983	Klosa
5,380,937		1/1995	Koehler et al.
5,758,095		5/1998	Albaum et al.
5,833,599		11/1998	Schrier et al.
5,845,255		12/1998	Mayaud
6,014,631		1/2000	Teagarden et al.
6,067,524		5/2000	Byerly et al.
6,112,182		8/2000	Akers et al.
6,204,245		3/2001	Siegel et al.
6,317,719		11/2001	Schrier et al.
6,356,873	B1	3/2002	Teagarden et al.
6,482,431	B2	11/2002	Smith

DOCKE

RM

6,780,889	B2	8/2004	Cook et al.
7,015,200	B2	3/2006	Mamelak et al.
7,072,840	B1	7/2006	Mayaud
7,262,219	B2	8/2007	Cook et al.
7,572,605	B2	8/2009	Mamelak et al.
7,668,730	B2	2/2010	Reardan et al.
7,765,106	B2	7/2010	Reardan et al.
7,765,107	B2	7/2010	Reardan et al.
7,797,171	B2	9/2010	Reardan et al.
7,851,506		12/2010	
7,895,059	B2	2/2011	Reardan et al.
8,263,650		9/2012	Cook et al.
8,324,275		12/2012	
2003/0171270	A1*	9/2003	Civelli et al 514/12
2006/0018933	A1	1/2006	Vaya et al.
2008/0293698		11/2008	Johnson 514/220
2009/0137565	A1	5/2009	
2010/0112056	A1	5/2010	
2010/0160299		6/2010	
2011/0237664		9/2011	Dalton et al 514/522
2012/0076865	Al	3/2012	Allphin et al.

FOREIGN PATENT DOCUMENTS

DE	237 309	5/1985
GB	922 029	3/1963
GB	980 279	1/1965
GB	1 522 450	8/1978
WO	WO 2006/053186	5/2006
WO	WO 2010/053691	5/2010
WO	WO 2011/119839	9/2011
WO	WO 2011/139271	11/2011
WO	WO 2012/037457	3/2012

OTHER PUBLICATIONS

Arena et al., "Absorption of Sodium γ-Hydroxybutyrate and Its Prodrug γ-Butyrolactone: Relationship between In Vitro Transport and In Vivo Absorption," *J. Pharmaceutical Sciences*, 69(3): 356-358, 1980.

Auler et al., "Diclofenac Plasma Protein Binding: PK-PD Modelling in Cardiac Patients Submitted to Cardiopulmonary Bypass," *Braz. J. Med. Bio. Res.*, 30: 369-374, 1997.

(Continued)

Primary Examiner — Shirley V Gembeh (74) Attorney, Agent, or Firm — Jones Day

(57) ABSTRACT

One embodiment of the present invention is to improve the safety and efficacy of the administration of GHB or a salt thereof to a patient. It has been discovered that the concomitant administration of an MCT inhibitor, such as diclofenac, valproate, or ibuprofen, will affect GHB administration. For example, it has been discovered that diclofenac lowers the effect of GHB in the body, thereby potentially causing an unsafe condition. Furthermore, it has been discovered that valproate increases the effect of GHB on the body, thereby potentially causing an unsafe condition.

34 Claims, 10 Drawing Sheets

References Cited

(56)

OTHER PUBLICATIONS

Banerjee et al., "Presynaptic *Gamma*-Hydroxybutyric Acid (GHB) and *Gamma*-Aminobutyric Acid_B (GABA_B) Receptor-Mediated Release of GABA and glutamate (GLU) in Rat Thalamic Ventrobasal Nucleus (VB): A Possible Mechanism for the Generation of Absence-Like Seizures Induced by GHB," *J. Pharmacol. Exp. Ther.*, 273 (3): 1534-1543, 1995.

U.S. Appl. No. 13/739,886, filed Jan. 11, 2013, Allphin et al.

U.S. Appl. No. 61/317,212, filed Mar. 24, 2010, Allphin et al. Bédard et al., "Nocturnal γ-Hydroxybutyrate. Effect on Periodic Leg

Movements and Sleep Organization of Narcoleptic Patients," *Clin. Neuropharniacol.*, 12(1): 29-36, 1989.

Broughton et al., "The Treatment of Narcolepsy-Cataplexy with Nocturnal Gamma-Hydroxybutyrate," *Le Journal Canadien Des Sciences Neurologiques*, 6(1): 1-6, 1979.

Cash et al., " γ -Hydroxybutyrate Receptor Function Studied by the Modulation of Nitric Oxide Synthase Activity in Rat Frontal Cortex Punches," *Biochemical Pharmacology*, 58 (11): 1815-1819, 1999.

Dimitrijevic et al., "*Drosophila* GABA_B Receptors are Involved in Behavioral Effects of γ -Hydroxybutyric Acid (GHB)," *Eur. J. Pharmacol.*, 519 (3): 246-252, 2005.

Gallimberti et al., "Gamma-Hydroxybutyric Acid for Treatment of Alcohol Withdrawal Syndrome," *The Lancet*, Sep. 30: 787-789, 1989.

Gallimberti et al., "Gamma-Hydroxybutyric Acid in the Treatment of Alcohol Dependence: A Double-Blind Study," *Alcoholism: Clinical and Experimental Research*, 16(4): 673-676, 1992.

Gallimberti et al., "Gamma-Hydroxybutyric Acid for Treatment of Opiate Withdrawal Syndrome," *Neuropsychopharmacology*, 9(1): 77-81, 1993.

Gallimberti et al., "Clinical Efficacy of Gamma-Hydroxybutyric Acid in Treatment of Opiate Withdrawal," *Eur Arch Psychiatry Clin Neurosci*, 244: 113-114, 1994.

Gerra et al., "Flumazenil Effects on Growth Hormone Response to Gamma-Hydroxybutyric Acid," *Internat. Clin. Psychopharm.*, 9: 211-215, 1994.

Gessa et al., "Gamma-Hydroxybutyric Acid in the Treatment of Alcohol Dependence," *Clin. Neuropharm.—Supplement*, 15 (Suppl. 1, Pt. A): 303A-304A, 1992.

Gonzalez et al., "Drug Metabolism," in *Goodman & Gilman's The Pharmacological Basis of Therapeutics* (11th ed.), Brunton et al. (eds.), New York: McGraw-Hill, pp. 71-91, 2006.

Halestrap et al., "The *SLC16* Gene Family—From Monocarboxylate Transporters (MCTs) to Aromatic Amino Acid Transporters and Beyond," *Pflugers Arch.*, 447 (5): 619-628, 2004.

Hasan et al., "Pharmacokinetics of Diclofenac Sodium in Normal Man," *Pakistan Jour. Pharmaceutical Sciences*, 18(1): 18-24, 2005. Hasenbos et al., "Anaesthesia for bullectomy," Anaesthesia, 40: 977-980, 1985.

Hechler et al., "Extracellular Events Induced by γ-Hydroxybutyrate in Striatum: A Microdialysis Study," *J. Neurochem.*, 56 (3): 938-944, 1991.

Henry, Thomas R., "The History of Divalproex in Clinical Neuroscience," *Psychopharmacology Bulletin*, 37 (Suppl 2): 5-16, 2003.

Jazz Pharmaceuticals, Inc., "Annex I Summary of Product Characteristics," XYREM® SmPC European Package Insert available at: http://www.ema.europa.eu/docs/en_GB/document_library/

EPAR ____Product_Information/human/000593/WC500057103. pdf (downloaded May 3, 2013).

Jazz Pharmaceuticals, Inc., "XYREM® (sodium oxybate) oral solution Prescribing Information," XYREM® US Package Insert available at http://www.xyrem.com/xyrem-pi.pdf (downloaded May 3, 2013).

Kuriyama et al., "Blood—Brain Barrier to H³-γ-Aminobutyric Acid in Normal and Amino Oxyacetic Acid-Treated Animals," *Neuropharmacology*, 10: 103-108, 1971.

DOCKET

Laborit, H., "Gamma-Hydroxybutyrate, Succinic Semialdehyde and Sleep," Laboratoire d'Eutonologie, Hopital Boucicaut, Paris 15, France, pp. 257-274, 1973.

Ladinsky et al., Mode of Action of Gamma-Butyrolactone on the Central Cholinergic System, *Naunyn-Schmiedeberg's Arch. Pharmacal.*, 322: 42-48, 1983.

Lammers et al., "Gammahydroxybutyrate and Narcolepsy: A Double-Blind Placebo-Controlled Study," *Sleep*, 16(3); 216-220, 1993.

Lapierre et al., "The Effect of Gamma-Hydroxybutyratc: A Double-Blind Study of Normal Subjects," *Sleep Research*, 17: 99, 1988 (abstract).

Lapierre et al., "The Effect of Gamma-Hydroxybutyrate on Nocturnal and Diurnal Sleep of Normal Subjects: Further Considerations on REM Sleep—Triggering Mechanisms," *Sleep*, 13(1): 24-30, 1990.

Lee, C.R., "Evidence for the β -Oxidation of Orally Administered 4-Hydroxybutyrate in Humans," *Biochem. Med.*, 17, 284-291: 1977. Lettieri et al., "Improved Pharmacological Activity via Pro-Drug Modification: Comparative Pharmacokinetics of Sodium γ -Hydroxybutyrate and γ -Butyrolactone," *Research Communications in Chemical Pathology and Pharmacology*, 22(1): 107-118, 1978.

Maitre et al., "A Specific γ-Hydroxybutyrate Receptor Ligand Possesses both Antagonistic and Anticonvulsant Properties," *J. Pharmacol. Exp. Ther.*, 255 (2): 657-663, 1990.

Maitre et al., "Mécanismes d'action d'un medicament détourné: le γ -hydroxybutyrate" ('A mechanism for gamma-hydroxybutyrate (GHB) as a drug and a substance of abuse') (in French), *Med Sci* (Paris), 21 (3): 284-9, 2005.

Mamelak et al., "Sleep-Inducing Effects of Gammahydroxybutyrate," *The Lancet*, 302 (7824): 328-329, 1973.

Mamelak et al., "The Effects of γ-Hydroxybutyrate on Sleep," *Biol. Psychiatry*, 12(2): 273-288, 1977.

Mamelak et al., "Narcolepsy: A Family Study," *Biological Psychiatry*, 14: 821-834, 1979.

Mamelak et al., "Treatment of Narcolepsy and Sleep Apnea with Gammahydroxybutyrate: A Clinical and Polysomnographic Case Study," *Sleep*, 4(1): 105-111, 1981.

Mamelak, "Gammahydroxybutyrate: An Endogenous Regulator of Energy Metabolism," *Neuroscience and Biobehay. Reviews*, 13: 187-198, 1989.

Modi et al., "Dapoxetine has no Pharmacokinetic or Cognitive Interactions with Ethanol in Healthy Male Volunteers," *J. Clin. Pharmac.*, 47(3): 315-322, 2007.

Nema et al., "Excipients and Their Use in Injectable Products," *PDA J. Pharm. Sci. Technol.*, 51(4): 166-171, 1997.

Palatini et al., "Dose-Dependent Absorption and Elimination of Gamma-Hydroxybutyric Acid in Healthy Volunteers," *Eur. J. Clin. Pharmacol.*, 45: 353-356, 1993.

Rapeport et al., "Absence of a Sertraline-Mediated Effect on Digoxin Pharmacokinetics and Electrocardiographic Findings," J. Clin. Psychiatry, 57: 16-19, 1996.

Rapeport et al., "Absence of a Sertraline-Mediated Effect on the Pharmacokinetics and Pharmacodynamics of Carbamazepine," J. Clin. Psychiatry, 57: 20-23, 1996.

Rapeport et al., "Absence of Effect of Sertraline on the Pharmacokinetics and Pharmacodynamics of Phenytoin," *J. Clin. Psychiatry*, 57: 24-28, 1996.

Rosenberg, G., "The Mechanisms of Action of Valproate in Neuropsychiatric Disorders: Can We See the Forest for the Trees?" *Cel. Mol. Life Sci.*, 64 (16): 2090-2103. 2007.

Roth et al., "γ-Butyrolactone and γ-Hydroxybutyric Acid—I Distribution and Metabolism," *Biochemical Pharmacology*, 15: 1333-1348, 1966.

Roth et al., "γ-Butyrolactonc and γ-Hydroxybutyric Acid—II The Pharmacologically Active Form," *Int. J. Neropharmacol.*, 5: 421-428, 1966.

Scharf et al., "The Effects and Effectiveness of γ-Hydroxybutyrate in Patients with Narcolepsy," *J. Clin. Psychiatry*, 46(6): 222-225, 1985. Scrima et al., "Gamma-Hydroxybutyrate Effects on Cataplexy and Sleep Attacks in Narcoleptics," *Sleep Res.*, 16: 134, 1987, Abstract.

Find authenticated court documents without watermarks at docketalarm.com.

References Cited

(56)

OTHER PUBLICATIONS

Scrima et al., "Efficacy of Gamma-Hydroxybutyrate versus Placebo in Treating Narcolepsy-Cataplexy: Double-Blind Subjective Measured," Biol. Psychiatry, 26: 331-343, 1989.

Scrima et al., "The Effects of \gamma-Hydroxybutyrate on the Sleep of Narcolepsy Patients: A Double-Blind Study," Sleep, 13(6): 479-490, 1990.

Sériès et al., "Effects of Enhancing Slow-Wave Sleep by Gamma-Hydroxybutyrate on Obstructive Sleep Apnea," Am. Rev. Respir. Dis., 1378-1383, 1992.

Smolders et al., "Tonic GABA-ergic Modulation of Striatal Dopamine Release Studied by In Vivo Microdialysis in the Freely Moving Rat," Eur. J. Pharmacol., 284 (1-2): 83-91, 1995

Strong, "y-Hydroxybutyric Acid and Intracranial Pressure," The Lancet, vol. 1: No. 8389, 1984.

Van Den Bogert et al., "Placentatransfer of 4-Hydroxybutyric Acid in Man," Anesthesiology and Intensive Care Medicine, 110: 55-64, 1978.

Vickers, M.D., "Gammahydroxybutyric Acid," Int. Anesth. Clinic, 7: 75-89, 1969.

Waszkielewicz et al., "q-Hydrobutyric Acid (GHB) and its Chemical Modifications: A Review of the GHBergic System," Pol J Pharmacol., 56 (1): 43-49, 2004.

Wesnes et al., "Moxonidine and Cognitive Function: Interactions with Moclobemide and Lorazepam," Eur. J. Clinic. Pharmacol., 52: 351-358, 1997.

Wesnes et al., "The Memory Enhancing Effects of a Ginkgo biloba/ Panax ginseng Combination in Healthy Middle-Aged Volunteers," *Psychopharmacology*, 152: 353-361, 2000. Williams et al., "Absence of Effect of Sertraline on Time-Based Sensitization of Cognitive Impairment with Haloperidol," *J. Clinic.*

Psych., 57, 7-11, 1996.

Wu et al., " γ -Hydroxybutyric acid (GHB) and γ -aminobutyric acid_B receptor (GABA_BR) binding sites are distinctive from one another: molecular evidence," Neuropharmacology, 47 (8): 1146-56, 2004.

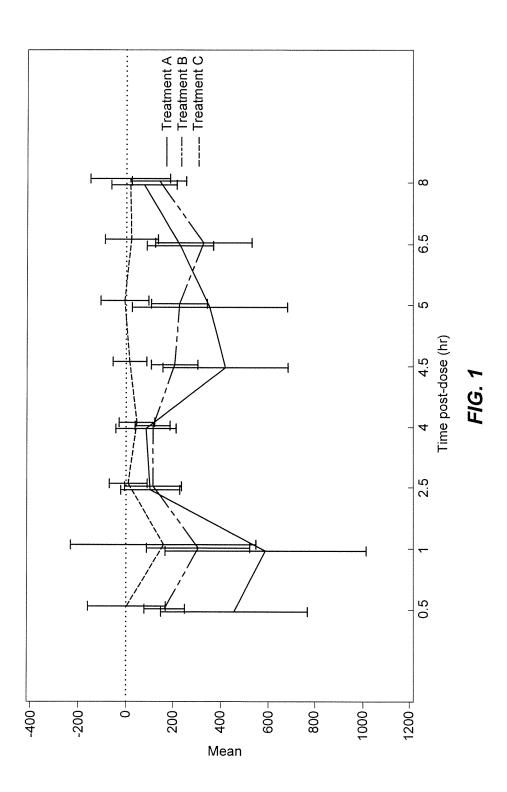
Yamada et al., "Effect of Butyrolactone and Gamma-Hydroxybutyrate on the EEG and Sleep Cycle in Man," Electroenceph. Clin. Neurophysiol., 22: 558-562, 1967.

United States Patent and Trademark Office, nonfinal Office Action mailed Nov. 15, 2013, in related U.S. Appl. No. 13/873,000.

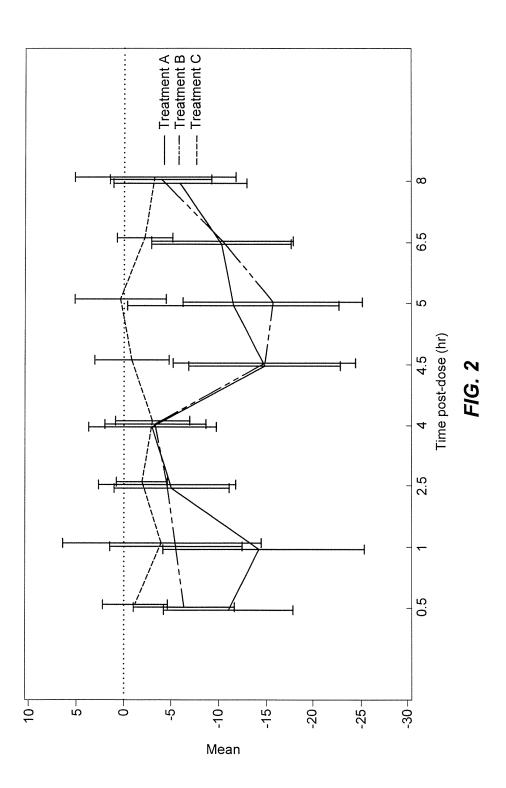
Wellendorph et al., "Phenylacetic acids and the structurally related non-steroidal anti-inflammatory drug diclofenac bind to specific c-hydroxybutyric acid sites in rat brain," Fundamental & Clinical Pharmacology, 23: 207-213, 2009.

Orphan Medical, Inc., NDA 21196, Major Amendment, filed Mar. 26, 2001, "Review and Evaluation of Clinical Data," http://www.fda. gov/ohrms/dockets/ac/01/briefing/3754b1_02_section%204.PDF (as downloaded on Mar. 4, 2014).

* cited by examiner



DOCKET ALARM Find authenticated court documents without watermarks at <u>docketalarm.com</u>.



DOCKET A L A R M Find authenticated court documents without watermarks at <u>docketalarm.com</u>.

DOCKET A L A R M



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.