



US009629965B2

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

(10) **Patent No.:** **US 9,629,965 B2**
(45) **Date of Patent:** ***Apr. 25, 2017**

(54) **NASAL DRUG PRODUCTS AND METHODS OF THEIR USE**

(71) Applicant: **Opiant Pharmaceuticals, Inc.**, Santa Monica, CA (US)

(72) Inventors: **Roger Crystal**, Santa Monica, CA (US); **Michael Brenner Weiss**, New York, NY (US)

(73) Assignee: **Opiant Pharmaceuticals, Inc.**, Santa Monica, 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.: **15/335,145**

(22) Filed: **Oct. 26, 2016**

(65) **Prior Publication Data**

US 2017/0043107 A1 Feb. 16, 2017

Related U.S. Application Data

(63) Continuation of application No. 14/942,344, filed on Nov. 16, 2015, now Pat. No. 9,480,644, which is a continuation-in-part of application No. 14/659,472, filed on Mar. 16, 2015, now Pat. No. 9,211,253.

(60) Provisional application No. 61/953,379, filed on Mar. 14, 2014.

(51) **Int. Cl.**

A61M 31/00 (2006.01)
A61M 5/00 (2006.01)
A61F 13/00 (2006.01)
A61K 31/56 (2006.01)
A61M 11/00 (2006.01)
A61K 9/00 (2006.01)
A61K 31/485 (2006.01)
A61K 47/02 (2006.01)
A61K 47/18 (2017.01)
A61K 9/08 (2006.01)
A61M 15/08 (2006.01)

(52) **U.S. Cl.**

CPC **A61M 11/006** (2014.02); **A61K 9/0043** (2013.01); **A61K 9/08** (2013.01); **A61K 31/485** (2013.01); **A61K 47/02** (2013.01); **A61K 47/18** (2013.01); **A61K 47/183** (2013.01); **A61K 47/186** (2013.01); **A61M 15/08** (2013.01); **A61M 31/00** (2013.01)

(58) **Field of Classification Search**

None
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,987,136 A 1/1991 Kreek et al.
5,866,154 A 2/1999 Bahal et al.
9,192,570 B2 11/2015 Wyse et al.
9,211,253 B2 12/2015 Crystal et al.
9,468,747 B2 10/2016 Crystal et al.
9,480,644 B2 11/2016 Crystal et al.
2003/0077300 A1 4/2003 Wermeling
2006/0120967 A1 6/2006 Namburi et al.
2009/0017102 A1 1/2009 Stinchcomb et al.
2010/0113495 A1 5/2010 Wermeling et al.
2010/0168147 A1 7/2010 Chapleo et al.
2010/0331354 A1 12/2010 Wermeling
2011/0046172 A1 2/2011 Chapleo et al.
2012/0270895 A1 10/2012 Wermeling
2013/0023825 A1 1/2013 Edwards et al.
2016/0008277 A1 1/2016 Crystal et al.
2016/0303041 A1 10/2016 Keegan et al.

FOREIGN PATENT DOCUMENTS

CN 1575795 2/2005
EP 1681057 B1 8/2008
WO WO 8203768 A1 11/1982
WO WO 9830211 A1 7/1998
WO WO 0062757 A1 10/2000
WO WO 0074652 A1 12/2000
WO WO 0158447 A1 8/2001
WO WO 0182931 A1 11/2001
WO WO 0211778 A1 2/2002
WO WO 03084520 A2 10/2003
WO WO 2004054511 A2 7/2004
WO WO 2005020906 A2 3/2005
WO WO 2006089973 A2 8/2006
WO WO 2007083073 A1 7/2007
WO WO 2009040595 A1 2/2009
WO WO 2012026963 A2 3/2012
WO WO 2012156317 A2 11/2012
WO WO 2013128447 A1 9/2013
WO WO 2014016653 A1 1/2014
WO WO 2015095644 A1 6/2015
WO WO 2015136373 A1 9/2015
WO WO 2015136373 A3 9/2015
WO WO 2016007729 A1 1/2016
WO WO 2016007729 A3 1/2016

OTHER PUBLICATIONS

Aptar UnitDose and BiDose product information sheet, available at www.aptar.com/docs/pharma-prescription/uds-bds-datasheet.pdf, publication date unknown, last accessed Mar. 26, 2015.

(Continued)

Primary Examiner — Jeffrey T Palenik

(74) *Attorney, Agent, or Firm* — Dennis A. Bennett; Cynthia Hathaway

(57) **ABSTRACT**

Drug products adapted for nasal delivery, comprising a pre-primed device filled with a pharmaceutical composition comprising an opioid receptor antagonist, are provided. Methods of treating opioid overdose or its symptoms with the inventive drug products are also provided.

(56)

References Cited

OTHER PUBLICATIONS

- Ashton H et al., "Best evidence topic report. Intranasal naloxone in suspected opioid overdose," *Emerg Med J* 23:3, 221-23 (published Mar. 2006).
- Bailey A M et al., "Naloxone for opioid overdose prevention: pharmacists' role in community-based practice settings," *Ann. Pharmacother* 48:5, 601-06 (published May 2014).
- Barton E D et al., "Efficacy of intranasal naloxone as a needleless alternative for treatment of opioid overdose in the prehospital setting," *J Emerg Med* 29:3, 265-71 (published Oct. 2005).
- Barton E D et al., "Intranasal administration of naloxone by paramedics," *Prehosp Emerg Care* 6:1, 54-58 (published Jan. 2002).
- Crystal r. et al., Nasal drug products and methods of their use, Lightlake Therapeutics, Inc., U.S. Pat. No. 9,211,253, Notice of Allowance, Oct. 9, 2015.
- Crystal r. et al., Nasal drug products and methods of their use, Lightlake Therapeutics, Inc., U.S. Pat. No. 9,211,253, Notice of Allowance, Nov. 9, 2015.
- Crystal r. et al., Nasal drug products and methods of their use, Lightlake Therapeutics, Inc., U.S. Pat. No. 9,468,747, Notice of Allowance, Apr. 12, 2016.
- Crystal r. et al., Nasal drug products and methods of their use, Lightlake Therapeutics, Inc., U.S. Pat. No. 9,468,747, Notice of Allowance, Jul. 26, 2016.
- Crystal r. et al., Nasal drug products and methods of their use, Lightlake Therapeutics, Inc., U.S. Pat. No. 9,480,644, Examiner initiated interview summary, Mar. 31, 2016.
- Crystal r. et al., Nasal drug products and methods of their use, Lightlake Therapeutics, Inc., U.S. Pat. No. 9,480,644, Notice of Allowance, Mar. 31, 2016.
- Crystal r. et al., Nasal drug products and methods of their use, Lightlake Therapeutics, Inc., U.S. Pat. No. 9,480,644, Notice of Allowance, Jul. 7, 2016.
- Doe-Simkins M et al., "Saved by the nose: bystander-administered intranasal naloxone hydrochloride for opioid overdose," *Am J Public Health* 99:5, 788-91 (published May 2009).
- Dowling J et al., "Population pharmacokinetics of intravenous, intramuscular, and intranasal naloxone in human volunteers," *Ther Drug Monit* 30:4 490-96 (published Aug. 2008).
- Heard C et al., "Intranasal flumazenil and naloxone to reverse over-sedation in a child undergoing dental restorations," *Paediatr Anaesth* 19:8 795-99 (published Aug. 2009).
- Kelly A M et al., "Intranasal naloxone for life threatening opioid toxicity," *Emerg Med J* 19:4, 375 (published Jul. 2002).
- Kelly A M et al., "Randomised trial of intranasal versus intramuscular naloxone in prehospital treatment for suspected opioid overdose," *Med J Aust* 182:1 24-27 (published Jan. 3, 2005).
- Kerr D et al., "Randomized controlled trial comparing the effectiveness and safety of intranasal and intramuscular naloxone for the treatment of suspected heroin overdose," *Addiction* 104:12, 2067-74 (Epub Nov. 9, 2009).
- Krieter P et al., Pharmacokinetic Properties and Human Use Characteristics of an FDA Approved Intranasal Naloxone Product for the Treatment of Opioid Overdose, *J Clin Pharmacol*, 2016, pp. 1-11.
- Loimer N et al., "Nasal administration of naloxone for detection of opiate dependence," *J Psychiatr Res* 26:1, 39-43 (published Jan. 1992).
- Loimer N et al., "Nasal administration of naloxone is as effective as the intravenous route in opiate addicts," *Int J Addict* 29:6, 819-27 (published Apr. 1994).
- Merlin M A et al., "Intranasal naloxone delivery is an alternative to intravenous naloxone for opioid overdoses," *Am J Emerg Med* 28:3, 296-303 (Epub Jan. 28, 2010).
- Robertson T M, "Intranasal naloxone is a viable alternative to intravenous naloxone for prehospital narcotic overdose," *Prehosp Emerg Care* 13:4, 512-15 (Published Oct. 2009).
- Walley A Y et al., "Opioid overdose prevention with intranasal Walley, A Y et al., "Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis," *BMJ* 346:f174, (Published Jan. 31, 2013).
- Weber J M et al., "Can nebulized naloxone be used safely and effectively by emergency medical services for suspected opioid overdose?" *Prehosp Emerg Care* 16:2, 289-92 (Epub Dec. 22, 2011).
- Wermeling D P et al., "A response to the opioid overdose epidemic: naloxone nasal spray," *Drug Delivery Transl. Res.* 3:1, 63-74 (published Feb. 1, 2013).
- Wermeling D P et al., "Opioid harm reduction strategies: focus on expanded access to intranasal naloxone," *Pharmacotherapy* 30:7, 627-31, 2010.
- Teva Pharmaceuticals USA, Inc., "Notice of ANDA No. 209522 naloxone hydrochloride nasal spray, 4mg/spray, with paragraph IV certification concerning U.S. Pat. No. 9,211,253", dated Sep. 13, 2016.
- Adapt Pharma Operations Limited, et al. v. Teva Pharmaceuticals USA, Inc., et al.*, U.S. District Court for the District of New Jersey. Civ. Action No. 2:16-cv-07721 (Nov. 26, 2016); Exhibit A U.S. Pat. 9,211,253.
- Adapt Pharma Operations Limited, et al. v. TEVA Pharmaceuticals USA, Inc., et al.*, U.S. District Court for the District of New Jersey. Civ. Action No. 2:17-cv-00864 (Feb. 8, 2017); U.S. Pat. 9,468,747.
- Beletsky, L. et al., "Physicians' Knowledge of and Willingness to Prescribe Naloxone to Reverse Accidental Opiate Overdose: Challenges and Opportunities." *Journal of Urban Health: Bulletin of the New York Academy of Medicine*, 84(1):126-136 (published 2006). Corrected Notice Allowance, U.S. Appl. No. 14/659,472, Nov. 2015, 9 pgs.
- Corrected Notice of Allowance and Fees Due, dated Nov. 9, 2015 in U.S. Appl. No. 14/659,472, 9 pgs.
- Crystal R. et al., Nasal drug products and methods of their use, Lightlake Therapeutics, Inc., U.S. Appl. No. 14/659,472, Notice of Allowance, Nov. 9, 2015.
- Crystal R. et al., Nasal drug products and methods of their use, Lightlake Therapeutics, Inc., U.S. Appl. No. 14/942,344, Notice of Allowance, Mar. 31, 2016.
- Crystal R. et al., Nasal drug products and methods of their use, Lightlake Therapeutics, Inc., U.S. Appl. No. 14/950,707, Notice of Allowance, Apr. 12, 2016.
- Djupesland; *Drug Deliv. and Transl. Res.* (2013) 3:42-62.
- International Search Report (ISR), dated Sep. 2, 2015 in International Application No. PCT/IB2015/000941, 4 pgs.
- International Search Report and Written Opinion for Application No. IB/2015/000941; Sep. 2, 2015; 11 pages.
- International Search Report and Written Opinion for WO/2015/136373; Sep. 2, 2015; 10 pages.
- International Search Report and Written Opinion for WO/2016/007729; Dec. 4, 2015; 16 pages.
- Krieter P et al., Pharmacokinetic Properties and Human Use Characteristics of an FDA-Approved Intranasal Naloxone Product for the Treatment of Opioid Overdose, *J Clin Pharmacol*. Oct. 2016;56 (10)1243-1253.
- Kundoor et al.; Effect of formulation- and administration-related variables on deposition pattern of nasal spray pumps evaluated using a nasal, *Pharm. Res.* (2011) 28:1895-1904.
- Makidon PE, et al., Characterization of stability and nasal delivery systems for immunization with nanoemulsion-based vaccines, *J Aerosol Med Pulm Drug Deliv.* Apr. 2010;23(2):77-89.
- Notice of Allowance, U.S. Appl. No. 14/659,472, Oct. 9, 2015, 9 pgs.
- TEVA Pharmaceuticals USA, Inc., Notice of ANDA No. 209522 naloxone hydrochloride nasal spray, 4mg/spray, with paragraph IV certification concerning U.S. Pat. No. 9,468,747, dated Dec. 29, 2016.
- U.S. Appl. No. 15/268,066, filed Sep. 16, 2016, Nasal drug products and methods of their use, Keegan F. et al.
- U.S. Appl. No. 15/415,221, filed Jan. 25, 2017, Nasal drug products and methods of their use, Keegan F. et al.

FIG. 1

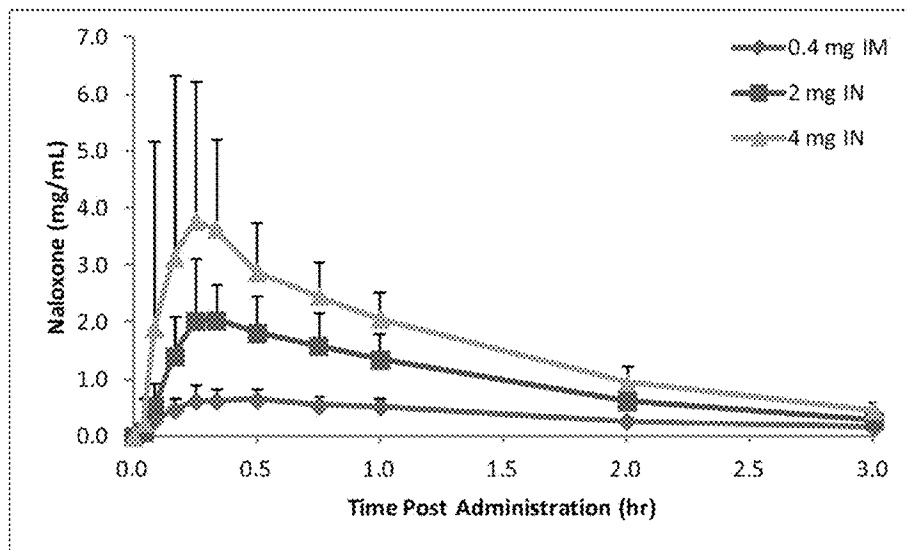


FIG. 2

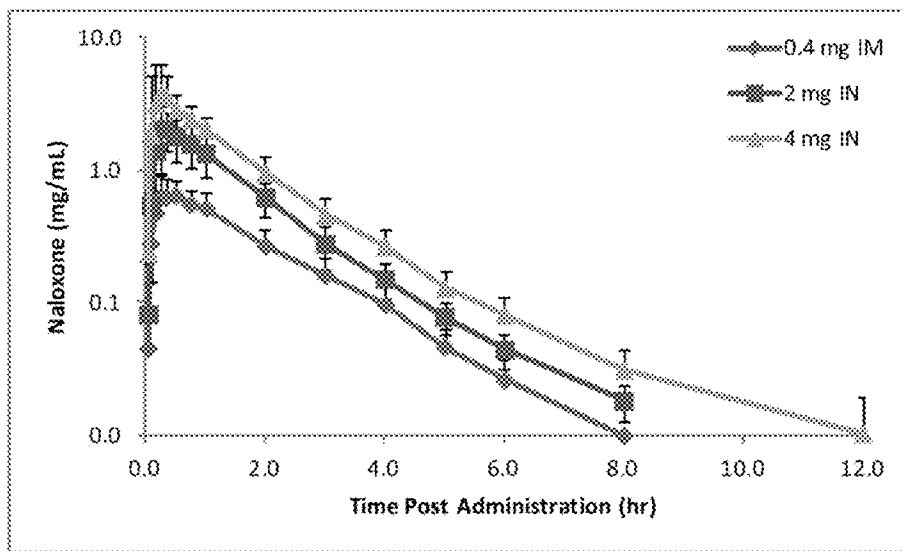
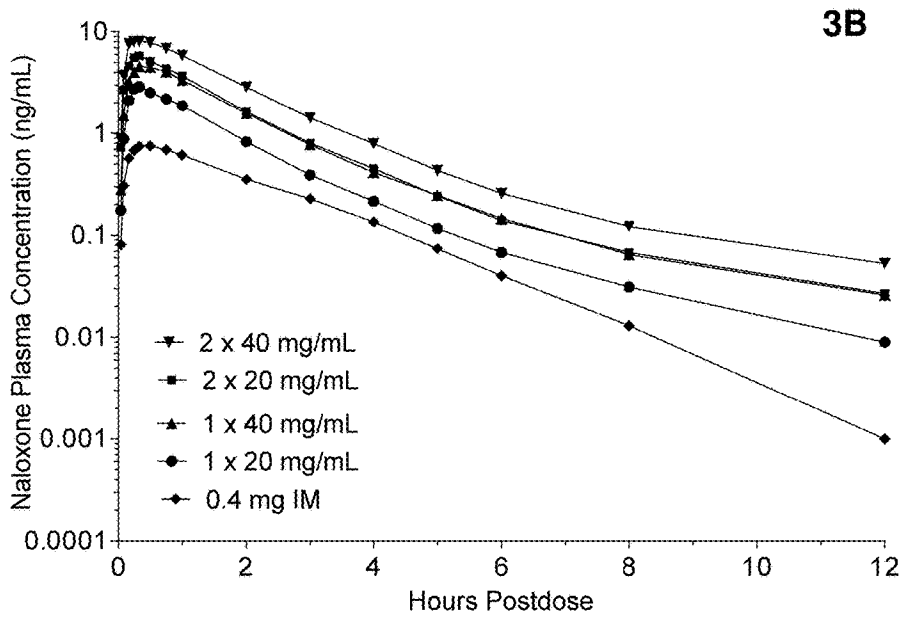
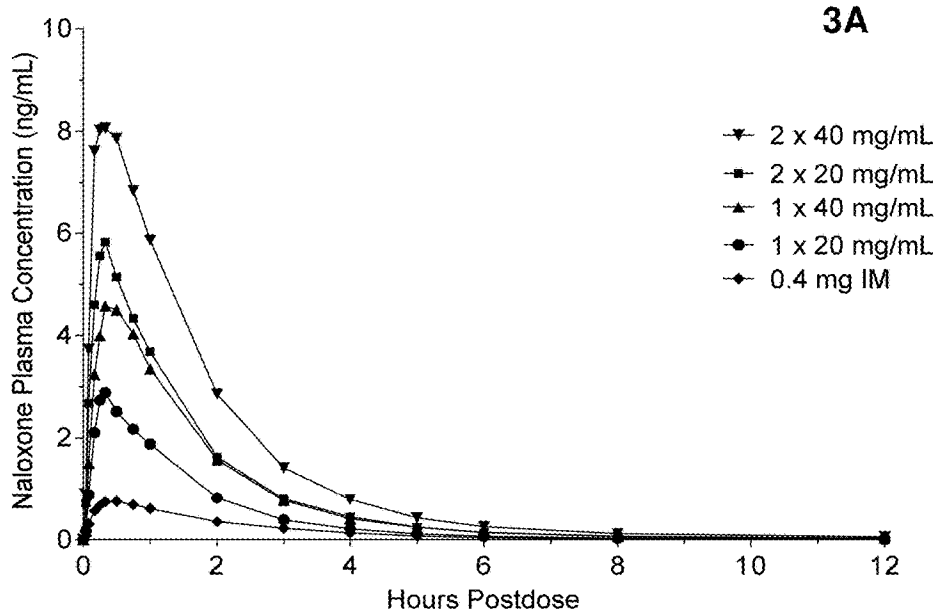


FIG. 3



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.