



US008598219B2

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

(10) **Patent No.:** **US 8,598,219 B2**  
(45) **Date of Patent:** **\*Dec. 3, 2013**

(54) **LIQUID PHARMACEUTICAL FORMULATIONS OF PALONOSETRON**  
(71) Applicants: **Helsinn Healthcare S.A.**, Lugano (CH); **Roche Palo Alto LLC**, Palo Alto, CA (US); **Simone Macciocchi**, Melide (CH); **Giulio Macciocchi**, Breganzona (CH)  
(72) Inventors: **Giorgio Calderari**, Rancate (CH); **Daniele Bonadeo**, Casalzuigno (IT); **Roberta Cannella**, Varese (IT); **Alberto Macciocchi**, Melide (CH); **Andrew Miksztal**, Palo Alto, CA (US); **Thomas Malefyt**, Carmel Valley, CA (US); **Kathleen M Lee**, Palo Alto, CA (US); **Carmine Panuccio**, Casnate con Bernat (IT)  
(73) Assignees: **Helsinn Healthcare SA**, Lugano/Pazzallo (CH); **Roche Palo Alto LLC**, Palo Alto, CA (US)

5,011,846 A 4/1991 Gittos et al.  
5,034,398 A 7/1991 King  
5,202,333 A 4/1993 Berger et al.  
5,240,954 A 8/1993 Tyers et al.  
5,272,137 A 12/1993 Blase et al.  
5,344,658 A 9/1994 Collin  
5,578,628 A 11/1996 Tyers et al.  
5,578,632 A 11/1996 Tyers et al.  
5,622,720 A 4/1997 Collin  
5,854,270 A 12/1998 Gambhir  
5,922,749 A 7/1999 Tyers et al.  
5,955,488 A 9/1999 Winterborn  
6,063,802 A 5/2000 Winterborn  
6,132,758 A 10/2000 Munayyer et al.  
6,284,749 B1 9/2001 Castillo et al.  
6,287,592 B1 9/2001 Dickinson  
6,294,548 B1 9/2001 James  
6,699,852 B2 3/2004 Robichaud  
7,109,339 B2 9/2006 Lee et al.  
7,947,724 B2 5/2011 Calderari et al.  
7,947,725 B2 5/2011 Calderari et al.  
7,960,424 B2 6/2011 Calderari et al.  
8,518,981 B2 8/2013 Calderari et al.  
2001/0020029 A1 9/2001 James  
2003/0095926 A1 5/2003 Dugger, III

(\* ) 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.

**FOREIGN PATENT DOCUMENTS**

EP 0 512 400 A1 4/1992  
WO WO-03100091 12/2003  
WO WO-2004045615 6/2004  
WO WO-2004067005 8/2004  
WO WO-2004703714 9/2004

(21) Appl. No.: **13/901,437**

(22) Filed: **May 23, 2013**

(65) **Prior Publication Data**

US 2013/0261592 A1 Oct. 3, 2013

**Related U.S. Application Data**

(63) Continuation-in-part of application No. 13/087,012, filed on Apr. 14, 2011, now Pat. No. 8,518,981, which is a continuation of application No. 11/186,311, filed on Jul. 21, 2005, now Pat. No. 7,947,724, which is a continuation of application No. PCT/EP2004/000888, filed on Jan. 30, 2004.

(60) Provisional application No. 60/444,351, filed on Jan. 30, 2003.

(51) **Int. Cl.**  
**A01N 43/52** (2006.01)

(52) **U.S. Cl.**  
USPC ..... **514/397**

(58) **Field of Classification Search**  
USPC ..... 514/397  
See application file for complete search history.

(56) **References Cited**

**U.S. PATENT DOCUMENTS**

4,695,578 A 9/1987 Coates et al.  
4,753,789 A 6/1988 Tyers et al.  
4,886,808 A 12/1989 King  
4,906,755 A 3/1990 Gittos

**OTHER PUBLICATIONS**

Center for Drug Evaluation and Research (Sep. 2002).\*  
R. M. Eglén et al., "Pharmacological characterization of RS 25259-197, a novel and selective 5-HT3 receptor antagonist, in vivo," Br. J. Pharmacology 114:860-866 (1995).  
Chelly, Jacques et al., Oral RS-25259 Prevents Postoperative Nausea and Vomiting Following Laparoscopic Surgery, Anesthesiology, 1996, vol. 85, No. 3A, p. A21.  
Sorbe, Bengt, 5-HT-3 Receptor Antagonists as Antiemetic Agents in Cancer Chemotherapy, extracted from Expert Opinion on Investigational Drugs, 1996, vol. 5 No. 4, pp. 389-407.  
Gaster, Laramie M. and King, Frank D., Serotonin 5-HT3 and 5-HT4 Receptor Antagonists, extracted from Medicinal Research Reviews, 1997 vol. 17, No. 2, pp. 163-214.  
Tang, Jun et al., "Efficacy of RS-25259, a Novel 5-HT3 Antagonist, In the Prevention of Postoperative Nausea and Vomiting after Major Gynecologic Surgery," Anesthesiology, 1997, vol. 85, No. 3 suppl. p. A329.  
Tang, Jun et al., The Efficacy of RS-25259, a Long-Acting Selective 5-HT3 Receptor Antagonist, for Preventing Postoperative Nausea and Vomiting After Hysterectomy Procedures, Anesthesia and Analgesia, 1998, vol. 87, pp. 462-467.  
Adis R&D Profile, Palonosetron RS 25259 197, Drugs in R&D, Oct. 1999, vol. 2, No. 4, pp. 251-252.

(Continued)

*Primary Examiner* — Shirley Gembeh  
(74) *Attorney, Agent, or Firm* — Clark G. Sullivan; Troutman Sanders LLP

(57) **ABSTRACT**

The present invention relates to shelf-stable liquid formulations of palonosetron for reducing chemotherapy and radiotherapy induced emesis with palonosetron. The formulations are particularly useful in Dr. Reddy's Laboratories, Ltd., et al.  
oral liquid medicaments.



US008598219B2

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

(10) **Patent No.:** **US 8,598,219 B2**  
(45) **Date of Patent:** **\*Dec. 3, 2013**

(54) **LIQUID PHARMACEUTICAL FORMULATIONS OF PALONOSETRON**  
(71) Applicants: **Helsinn Healthcare S.A.**, Lugano (CH); **Roche Palo Alto LLC**, Palo Alto, CA (US); **Simone Macciocchi**, Melide (CH); **Giulio Macciocchi**, Breganzona (CH)  
(72) Inventors: **Giorgio Calderari**, Rancate (CH); **Daniele Bonadeo**, Casalzuigno (IT); **Roberta Cannella**, Varese (IT); **Alberto Macciocchi**, Melide (CH); **Andrew Miksztal**, Palo Alto, CA (US); **Thomas Malefyt**, Carmel Valley, CA (US); **Kathleen M Lee**, Palo Alto, CA (US); **Carmine Panuccio**, Casnate con Bernat (IT)  
(73) Assignees: **Helsinn Healthcare SA**, Lugano/Pazzallo (CH); **Roche Palo Alto LLC**, Palo Alto, CA (US)

5,011,846 A 4/1991 Gittos et al.  
5,034,398 A 7/1991 King  
5,202,333 A 4/1993 Berger et al.  
5,240,954 A 8/1993 Tyers et al.  
5,272,137 A 12/1993 Blase et al.  
5,344,658 A 9/1994 Collin  
5,578,628 A 11/1996 Tyers et al.  
5,578,632 A 11/1996 Tyers et al.  
5,622,720 A 4/1997 Collin  
5,854,270 A 12/1998 Gambhir  
5,922,749 A 7/1999 Tyers et al.  
5,955,488 A 9/1999 Winterborn  
6,063,802 A 5/2000 Winterborn  
6,132,758 A 10/2000 Munayyer et al.  
6,284,749 B1 9/2001 Castillo et al.  
6,287,592 B1 9/2001 Dickinson  
6,294,548 B1 9/2001 James  
6,699,852 B2 3/2004 Robichaud  
7,109,339 B2 9/2006 Lee et al.  
7,947,724 B2 5/2011 Calderari et al.  
7,947,725 B2 5/2011 Calderari et al.  
7,960,424 B2 6/2011 Calderari et al.  
8,518,981 B2 8/2013 Calderari et al.  
2001/0020029 A1 9/2001 James  
2003/0095926 A1 5/2003 Dugger, III

(\* ) 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.

**FOREIGN PATENT DOCUMENTS**

EP 0 512 400 A1 4/1992  
WO WO-03100091 12/2003  
WO WO-2004045615 6/2004  
WO WO-2004067005 8/2004  
WO WO-2004703714 9/2004

(21) Appl. No.: **13/901,437**

(22) Filed: **May 23, 2013**

(65) **Prior Publication Data**

US 2013/0261592 A1 Oct. 3, 2013

**Related U.S. Application Data**

(63) Continuation-in-part of application No. 13/087,012, filed on Apr. 14, 2011, now Pat. No. 8,518,981, which is a continuation of application No. 11/186,311, filed on Jul. 21, 2005, now Pat. No. 7,947,724, which is a continuation of application No. PCT/EP2004/000888, filed on Jan. 30, 2004.

(60) Provisional application No. 60/444,351, filed on Jan. 30, 2003.

(51) **Int. Cl.**  
**A01N 43/52** (2006.01)

(52) **U.S. Cl.**  
USPC ..... **514/397**

(58) **Field of Classification Search**  
USPC ..... 514/397  
See application file for complete search history.

(56) **References Cited**

**U.S. PATENT DOCUMENTS**

4,695,578 A 9/1987 Coates et al.  
4,753,789 A 6/1988 Tyers et al.  
4,886,808 A 12/1989 King  
4,906,755 A 3/1990 Gittos

**OTHER PUBLICATIONS**

Center for Drug Evaluation and Research (Sep. 2002).\*  
R. M. Eglén et al., "Pharmacological characterization of RS 25259-197, a novel and selective 5-HT3 receptor antagonist, in vivo," Br. J. Pharmacology 114:860-866 (1995).  
Chelly, Jacques et al., Oral RS-25259 Prevents Postoperative Nausea and Vomiting Following Laparoscopic Surgery, Anesthesiology, 1996, vol. 85, No. 3A, p. A21.  
Sorbe, Bengt, 5-HT-3 Receptor Antagonists as Antiemetic Agents in Cancer Chemotherapy, extracted from Expert Opinion on Investigational Drugs, 1996, vol. 5 No. 4, pp. 389-407.  
Gaster, Laramie M. and King, Frank D., Serotonin 5-HT3 and 5-HT4 Receptor Antagonists, extracted from Medicinal Research Reviews, 1997 vol. 17, No. 2, pp. 163-214.  
Tang, Jun et al., "Efficacy of RS-25259, a Novel 5-HT3 Antagonist, In the Prevention of Postoperative Nausea and Vomiting after Major Gynecologic Surgery," Anesthesiology, 1997, vol. 85, No. 3 suppl. p. A329.  
Tang, Jun et al., The Efficacy of RS-25259, a Long-Acting Selective 5-HT3 Receptor Antagonist, for Preventing Postoperative Nausea and Vomiting After Hysterectomy Procedures, Anesthesia and Analgesia, 1998, vol. 87, pp. 462-467.  
Adis R&D Profile, Palonosetron RS 25259 197, Drugs in R&D, Oct. 1999, vol. 2, No. 4, pp. 251-252.

(Continued)

*Primary Examiner* — Shirley Gembeh  
(74) *Attorney, Agent, or Firm* — Clark G. Sullivan; Troutman Sanders LLP

(57) **ABSTRACT**

The present invention relates to shelf-stable liquid formulations of palonosetron for reducing chemotherapy and radiotherapy induced emesis with palonosetron. The formulations are particularly useful in the preparation of intravenous and oral liquid medicaments.

(56)

## References Cited

## OTHER PUBLICATIONS

- Piraccini Gaia et al., An Interesting 5-HT<sub>3</sub> Receptor Antagonist Antiemetic for Patients Undergoing Chemotherapy-based Conditioning Regimens, *Blood*, Nov. 16, 2001, vol. 98, No. 11, part 2, p. 350b, abstract No. 5169.
- Stacher, Georg, Palonosetron Helsinn, *Current Opinion in Investigational Drugs*, Oct. 2002, vol. 3, No. 10, pp. 1502-1507.
- Navari, Rudolph M., Pathogenesis-Based Treatment of Chemotherapy-Induced Nausea and Vomiting—Two New Agents, *Journal of Supportive Oncology*, 2003, vol. 1(2), pp. 89-103.
- Chaitow, 1990, 3 pages.
- Opposition Brief filed by Dr. Reddy's Laboratories (UK) Limited, opposition to European Patent No. 1601359 B1 dated Jul. 7, 2009.
- Photolytic and oxidative degradation of an antiemetic agent, RG 12915 (Won C. M. et al., *International Journal of Pharmaceutics* 121, 95-105 (1995).
- Palonosetron: a phase II dose ranging study to assess over a 7 day period the single dose pharmacokinetic profile of palonosetron in patients receiving highly emetogenic chemotherapy. Piraccini et al., *Proc. Am. Soc. Clin. Oncol* 2002 21 Abs 449 (2002).
- Formulation and administration techniques to minimize injection pain and tissue damage associated with parenteral products. Larry A. Gatlin and Carol A. Brister Gatlin, from *Injectable Drug Development: Techniques to Reduce Pain and Irritation* (Edited by Pramod K. Gupta and Gayle A. Brazeau; published by Informa Health Care) 1999; ISBN 1574910957, 9781574910957, p. 401-421.
- Parenteral Dosage Forms. Joanne Broadhead, from Part 11—Early drug development, pharmaceutical preformulation and formulation: a practice guide from candidate drug selection to commercial dosage form (Edited by Mark Gibson; Published by Interpharma Press, 2001; ISBN 1574911201, 9781574911206), p. 331-353.
- Opposition Brief filed by Tecnimede Sociedade Tecnico-Medicinal S.A. in opposition to European Patent No. 1601359 B1, Jul. 8, 2009.
- Response brief filed by Helsinn Healthcare S.A. dated Jul. 13, 2007, in response to the communication pursuant to Art. 96(2) EPC of Jan. 3, 2007 regarding Serial No. 04 706 657.6-2123.
- European Patent Office official communication dated Jul. 19, 2006, regarding Serial No. 04 706 657.6.
- Response of Helsinn Healthcare S.A. dated Nov. 29, 2006, regarding EPO official communication date Jul. 19, 2006.
- Lachman et al., *The Theory and Practice of Industrial Pharmacy*, 1986, third edition, pp. 652-784.
- Declaration of Valentino J. Stella, Ph.D. dated Sep. 19, 2007.
- Opposition Brief filed by Martin Paul White, opposition to European Patent No. 1601359 B1, Jul. 8, 2009.
- Wong et al. (1995), *In British Journal of Pharmacology*, vol. 114, pp. 851-859.
- Cover page and pp. 642-644 and 783-784 of *The Theory and Practice of Industrial Pharmacy*, Third Edition, Lea and Febiger (1986).
- Cover page and pp. 514-515 of *Modern Pharmaceutics*, Second Edition, Marcel Dekker (1990).
- Cover page and pp. 142-143 of *Pharmaceutical Dosage Forms: Parenteral Medications* vol. 1, Second Edition, Marcel Dekker (1992).
- Mitsuo Matsumoto et al., "Yakuzaigaku Manual", 1st edition, Nanzando Co., Ltd. (1989) 2 pages.
- Michael J. Pikal, "Freeze Drying", *Encyclopedia of Pharmaceutical Technology*, Third Edition, Jan. 2007, pp. 1824-1825, vol. 3, Informa Pharmaceuticals and Healthcare.
- Daniele Bonadeo, "Supplemental Declaration of Daniele Bonadeo Under 37 C.F.R. 1.132", filed in U.S. Appl. No. 11/388,270, Jun. 8, 2009.
- Kranke et al., 2007 "Recent advances, trends, and economic considerations in . . ." *Expert Opinion Pharmacotherp.*, 8(18): 3217-3235.
- Morrow et al., 1995, "Progress in reducing nausea and emesis: Comparisons of ondansetron, granisetron, and tropisetron." *Cancer*, vol. 76, No. 3 pp. 343-357.
- USPTO Office Action, U.S. Appl. No. 11/129,839, Date Mailed Jan. 15, 2010.
- Israeli, Zafar H., "Clinical Pharmacology of Serotonin Receptor Type (5-HT<sub>3</sub>) Antagonists," *Curr. Med. Chem. Central Nervous System Agents*, 2001:1, 171-199.
- Barton (Citrate Buffer Calculation) 2000, 2 pages.
- USPTO Office Action, U.S. Appl. No. 11/201,035, Date Mailed Aug. 19, 2009.
- Response of Helsinn Healthcare to opposition of EP Serial No. 04 706 657.6, dated Feb. 11, 2010.
- Annex 1 (Statement of Walso Mossi, Ph.D.) to Response of Helsinn Healthcare to Opposition of EP Serial No. 04 706 657.6 dated Feb. 11, 2010.
- Annex 2 to Response of Helsinn Healthcare to Opposition of EP Serial No. 04 706 657.6 dated Feb. 11, 2010.
- Annex 3 to Response of Helsinn Healthcare to Opposition of EP Serial No. 04 706 657.6 dated Feb. 11, 2010.
- Summary of Product Characteristics for Aloxi 250 (2009).
- Scientific Discussion from the European Public Assessment Report for Aloxi (Palonosetron Hydrochloride) 2006.
- 6th Edition, *Handbook of Pharmaceutical Excipients* (2009), pp. 247-250 (RPS Publishing).
- Lewis, Gareth A (2006) 'Optimization Methods,' *Encyclopedia of Pharmaceutical Technology*, 1:1, 2452-2467.
- May 24, 2011 Para. IV notice from Teva Pharmaceuticals re '724 and '725 patents.
- May 24, 2011 Para. IV notice from Sandoz re '724 and '725 patents.
- May 24, 2011 Para. IV notice from Dr. Reddy's re '724 and '725 patents.
- Aug. 9, 2011 Para. IV notice from Dr. Reddy's re '424 patent.
- Aug. 19, 2011 Para. IV notice from Teva Pharmaceuticals re '424 patent.
- Sep. 22, 2011 Para. IV notice from Sandoz re '724, '725 and '424 patents.
- Jul. 8, 2011 Complaint for patent infringement (D. N.J. case No. 11-03962).
- Sep. 23, 2011 Complaint for patent infringement (D. N.J. case No. 11-5579).
- Aug. 31, 2011 Answer and counterclaim of Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc. (D. N.J. case No. 11-03962).
- Sep. 13, 2011 Sandoz Inc.'s answer to complaint for patent infringement and counterclaims (D. N.J. case No. 11-03962).
- Sep. 13, 2011 Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries Ltd.'s answer (D. N.J. case No. 11-03962).
- Oct. 5, 2011 Plaintiff's reply to answer and counterclaim of Dr. Reddy's Laboratories, Ltd. and Dr. Reddy Laboratories, Inc. (D. N.J. case No. 11-03962).
- Oct. 21, 2011 Plaintiff's reply to Sandoz Inc.'s answer to complaint for patent infringement and counterclaims (D. N.J. case No. 11-03962).
- Oct. 24, 2011 Answer and counterclaim of Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc. (D. N.J. case No. 11-5579).
- Oct. 24, 2011 Sandoz Inc.'s answer to complaint for patent infringement and counterclaims (D. N.J. case No. 11-5579).
- Oct. 27, 2011 Order consolidating the two cases (D. N.J. case No. 11-5579).
- Nov. 17, 2011 Plaintiffs' reply to answer and counterclaim of Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc. (D. N.J. case No. 11-03962).
- Nov. 17, 2011 Plaintiffs' reply to Sandoz Inc.'s answer to complaint for patent infringement and counterclaims (D. N.J. case No. 11-03962).
- Dec. 5, 2011 Teva Pharmaceuticals USA Inc. and Teva Pharmaceuticals Industries Ltd.'s answer to complaint for patent infringement of the '424 patent (D. N.J. case No. 11-03962).
- May 21, 2012 Defendants' opening claim construction brief (including exhibits 1-31).
- May 21, 2012 Plaintiffs' opening claim construction brief (including exhibits 1-15).

(56)

**References Cited**

## OTHER PUBLICATIONS

Jul. 20, 2012 Plaintiffs' responsive claim construction brief (including Exhibits A and B).

Sep. 7, 2012 Court transcript from Sep. 7, 2012 Markman hearing and Plaintiffs' PowerPoint presentation (D. N.J. case No. 11-03962).

Dec. 1, 2011 Sandoz Inc.'s invalidity contentions pursuant to L. Pat. R. 3.6(c) (D. N.J. case No. 11-03962).

Dec. 1, 2011 Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries, Ltd.'s invalidity contentions, pursuant to L. Pat. R. 3.6(c)(D. N.J. case No. 11-03962).

Dec. 1, 2011 Dr. Reddy's Laboratories, Ltd.'s and Dr. Reddy's Laboratories, Inc.'s invalidity contentions pursuant to L. Pat. R. 3.6(c) (D. N.J. case No. 11-03962).

Jan. 31, 2012 Plaintiffs' responses to defendants' invalidity contentions (D. N.J. case No. 11-03962).

Sep. 25, 2012 Sandoz Inc.'s first amended invalidity contentions pursuant to L. Pat. R. 3.6(c) (D. N.J. case No. 11-03962).

Nov. 19, 2012 Plaintiffs' responses to Sandoz Inc.'s first amended invalidity contentions (D. N.J. case No. 11-03962).

L.G. Wade Jr., *Organic Chemistry*, Ch. 19: Amines, pp. 867-936 (Prentice Hall 3d ed. 1995).

L. Lachman et al., *The Theory and Practice of Industrial Pharmacy*, pp. 642-644, 783-784 (Lea & Febiger 3d ed. 1986).

P.P. DeLuca et al., *Formulation of Small Volume Parenterals in Pharmaceutical Dosage Forms: Parenteral Medications*, vol. 1, Ch. 5, pp. 173-248 (Avis, Lieberman, Lachman eds., Marcel Dekker Inc. 2d ed. 1992).

C.M. Won et al, *Photolytic and Oxidative Degradation of an Antiemetic Agent*, RGI2915, *Int'l J Pharmaceutics* 121:95-105 (1995).

R.D. Clark et al., 2-(Quinuclidin-3-yl)pyrido-[4,3-b]indol-1-ones and Isoquinolin-1-ones. Potent Conformationally Restricted 5-HT<sub>3</sub> Receptor Antagonists, *J Med. Chem.* 36:2645-57 (1993).

L.A. Trissel, *Drug Stability and Compatibility Issues*, Handbook on Injectable Drugs, pp. XI-XVI (ASHP 7th ed. 1992).

J. Broadhead, *Parenteral Dosage Forms, Pharmaceutical Preformulation and Formulation: A Practical Guide from Candidate Drug Selection to Commercial Dosage Form*, Ch. 9, pp. 331-354 (Gibson ed., CRC Press 1st ed. 2001).

K.A. Connors et al., *Chemical Stability of Pharmaceuticals: A Handbook for Pharmacists* (John Wiley & Sons 2d ed. 1986).

Zofran®, in *The Physician's Desk Reference*, op. 1503-07 (5th ed. 2001).

Anzemet®, in *The Physician's Desk Reference*, pp. 680-683 (5th ed. 2001).

Kytril®, in *The Physician's Desk Reference*, pp. 3104-3106 (5th ed. 2001).

L.A. Trissel, Ondansetron HCl, in *Handbook on Injectable Drugs*, pp. 683-688 (ASHP 7th ed. 1992).

Navoban® (tropisetron HCl) Malaysian Prescribing Information (Sep. 2000).

Kytril® (granisetron HCl) South African Prescribing Information (Dec. 1993).

S. Motola and S. Agharkar, *Preformulation Research of Parenteral Medications, Pharmaceutical Dosage Forms: Parenteral Medications*, vol. 1, Ch. 4, pp. 115-172 (Avis, Lieberman, Lachman eds., Marcel Dekker Inc. 2d ed. 1992).

J. Wells, *Pharmaceutical Preformulation: The Physicochemical Properties of Drug Substances*, Ch. 5: Drug Stability, pp. 152-191 (Ellis Horwood Ltd. 1988).

J. Swarbrick and Boylan, *Encyclopedia of Pharmaceutical Technology, Excipients Chapter: Their Role in Parenteral Dosage Forms*, vol. 19(2):137-172 (Marcel Dekker, Inc. 2000).

Handbook of Pharmaceutical Excipients, 3d Ed., (Kibbe ed. Pharmaceutical Press 2000); pp. 140-143, 191-194, 324-238.

G. Stacher, Palonosetron (Helsinn), *Curro. Opin. Investig. Drugs*, 3(10) 1502-7 (2002).

Handbook of Modern Pharmaceutical Analysis, (S. Ahuja et al. ed.,

Jun. 8, 2009 Bonadeo Declaration, Exhibit 2.

Jun. 8, 2009 Bonadeo Declaration, Exhibit 3.

HELSON0117262-69 (2008).

HELSON0117270-312 (2012).

Feb. 13, 2007 Statutory Declaration of Daniele Bonadeo, with Exhibit A.

Nov. 21, 2007 Statutory Declaration of Giorgio Calderari, Daniele Bonadeo, Roberta Cannella, Enrico Braglia, and Riccardo Braglia. Reddy's Paragraph IV notice regarding all three patents (D. N.J. Case No. 12-2867), dated Mar. 30, 2012.

May 11, 2012 Complaint for patent infringement filed by Helsinn and Roche (D. N.J. Case No. 12-2867).

Jun. 26, 2012 Notice of Reddy's motion to dismiss (D. N.J. Case No. 12-2867).

Jun. 26, 2012 Dr. Reddy's Laboratories, Ltd.'s and Dr. Reddy's Laboratories, Inc.'s memorandum of law in support of their motion to dismiss or for summary judgment of non-infringement of U.S. patent No. 7,947,724 (D. N.J. Case No. 12-2867) (including Exhibits 1-10).

Aug. 16, 2012 Notice of Plaintiffs' cross-motion for partial summary judgment of infringement (D. N.J. Case No. 12-2867).

Aug. 6, 2012 Plaintiffs' opposition to Defendants' motion to dismiss or for summary judgment of noninfringement and cross-motion for partial summary judgment of infringement (D. N.J. Case No. 12-1867) (including exhibits 1-4).

Schöneich declaration (D. N.J. Case No. 12-2867) (Including Exhibits A and 1-24), dated Aug. 6, 2012.

Sep. 4, 2012 Reddy's brief in opposition to Plaintiffs' cross-motion for partial summary judgment and reply memorandum of law in further support of Reddy's motion to dismiss or for summary judgment of non-infringement (D. N.J. Case No. 12-2867) (Including Exhibits 1-4).

DeLuca Declaration (D. N.J. Case No. 12-2867) (Including exhibits A-J), dated Sep. 3, 2012.

Sep. 10, 2012 Plaintiffs' letter to Judge Cooper in response to Reddy's combined opposition to Plaintiffs' cross-motion for partial summary judgment and reply in support of Reddy's motion to dismiss or for summary judgment of noninfringement (D. N.J. Case No. 12-2867) (including exhibits A and B).

Sep. 14, 2012 Dr. Reddy's letter in response to Plaintiffs' Sep. 10, 2012 letter (D. N.J. Case No. 12-2867).

USPTO Office Action, U.S. Appl. No. 11/388,268, filed Mar. 24, 2006, Mail Date Mar. 29, 2010.

USPTO Non-Final Office Action, U.S. Appl. No. 11/186,311, mailed Aug. 30, 2006.

USPTO Non-Final Office Action, U.S. Appl. No. 11/186,311, mailed Oct. 5, 2007.

USPTO Non-Final Office Action, U.S. Appl. No. 11/186,311, mailed Oct. 6, 2008.

USPTO Final Office Action, U.S. Appl. No. 11/186,311, mailed May 20, 2009.

USPTO Advisory Action, U.S. Appl. No. 11/186,311, mailed Jul. 15, 2009.

USPTO Notice of Allowance and Fees Due, U.S. Appl. No. 11/186,311, mailed Mar. 4, 2011.

USPTO Notice of Allowability, U.S. Appl. No. 11/186,311, dated May 24, 2011.

USPTO Non-Final Office Action, U.S. Appl. No. 11/388,268, mailed Jul. 17, 2006.

USPTO Non-Final Office Action, U.S. Appl. No. 11/388,268, mailed Nov. 17, 2006.

USPTO Non-Final Office Action, U.S. Appl. No. 11/388,268, mailed Oct. 3, 2007.

USPTO Non-Final Office Action, U.S. Appl. No. 11/388,268, mailed Mar. 26, 2008.

USPTO Final Office Action, U.S. Appl. No. 11/388,268, mailed Nov. 12, 2008.

USPTO Non-Final Office Action, U.S. Appl. No. 11/388,268, mailed Jul. 15, 2009.

USPTO Notice of Allowance and Fees Due, U.S. Appl. No. 11/388,268, mailed Dec. 22, 2010.

(56)

**References Cited**

## OTHER PUBLICATIONS

- USPTO Non-Final Office Action, U.S. Appl. No. 11/388,269, mailed Nov. 17, 2006.
- USPTO Non-Final Office Action, U.S. Appl. No. 11/388,269, mailed Sep. 20, 2007.
- USPTO Non-Final Office Action, U.S. Appl. No. 11/388,269, mailed Jul. 9, 2008.
- USPTO Interview Summary, U.S. Appl. No. 11/388,269, dated Apr. 28, 2009.
- USPTO Final Office Action, U.S. Appl. No. 11/388,269, mailed May 20, 2009.
- USPTO Advisory Action, U.S. Appl. No. 11/388,269, mailed Jul. 15, 2009.
- USPTO Notice of Abandonment, U.S. Appl. No. 11/388,269, mailed Dec. 18, 2009.
- USPTO Non-Final Office Action, U.S. Appl. No. 11/388,270, mailed Jul. 13, 2006.
- USPTO Interview Summary, U.S. Appl. No. 11/388,270, dated Aug. 3, 2006.
- USPTO Non-Final Office Action, U.S. Appl. No. 11/388,270, mailed Nov. 16, 2006.
- USPTO Non-Final Office Action, U.S. Appl. No. 11/388,270, mailed Sep. 20, 2007.
- USPTO Interview Summary, U.S. Appl. No. 11/388,270, dated Dec. 14, 2007.
- USPTO Non-Final Office Action, U.S. Appl. No. 11/388,270, mailed Mar. 25, 2008.
- USPTO Final Office Action, U.S. Appl. No. 11/388,270, mailed Oct. 29, 2008.
- USPTO Advisory Action, U.S. Appl. No. 11/388,270, mailed Jan. 23, 2009.
- USPTO Non-Final Office Action, U.S. Appl. No. 11/388,270, mailed Jul. 9, 2009.
- USPTO Interview Summary, U.S. Appl. No. 11/388,270, dated Nov. 12, 2010.
- USPTO Notice of Allowance and Fees Due, U.S. Appl. No. 11/388,270, mailed Jan. 5, 2011.
- USPTO Non-Final Office Action, U.S. Appl. No. 13/087,012, mailed Mar. 12, 2012.
- USPTO Non-Final Office Action, U.S. Appl. No. 13/087,012, mailed Jul. 19, 2012.
- USPTO Interview Summary, U.S. Appl. No. 13/087,012, dated Feb. 15, 2013.
- USPTO Notice of Allowance and Fees Due, U.S. Appl. No. 13/087,012, mailed Feb. 27, 2013.
- USPTO Response to Amendment under Rule 312, U.S. Appl. No. 13/087,012, mailed Apr. 4, 2013.
- USPTO Non-Final Office Action, U.S. Appl. No. 11/129,839, mailed Jun. 10, 2008.
- Eisenberg et al. 2004, "Efficacy, safety and pharmacokinetics of palonosetron in patients receiving highly emetogenic cisplatin-based chemotherapy: a dose-ranging clinical study." *Annals of Oncology*, vol. 15, pp. 330-337.
- Mayron et al. 1996, "Stability and compatibility of granisetron hydrochloride in i.v. solutions and oral liquids and during simulated Y-site injection with selected drugs." *Am J Health-Sys Pharm*, 53: 294-304.
- Trissel et al. 1997, "Compatibility of granisetron hydrochloride with selected drugs during simulated Y-site administration." *Am J Health-Syst Pharm* 54: 56-60.
- USPTO Final Office Action, U.S. Appl. No. 11/129,839, mailed Mar. 17, 2009.
- USPTO Advisory Action, U.S. Appl. No. 11/129,839, mailed Jul. 22, 2009.
- USPTO Non-Final Office Action, U.S. Appl. No. 11/129,839, mailed Jan. 15, 2010.
- USPTO Examiner Interview Summary, U.S. Appl. No. 11/129,839, mailed Nov. 9, 2010.
- USPTO Notice of Abandonment, U.S. Appl. No. 11/129,839, mailed Apr. 18, 2011.
- USPTO Non-Final Office Action, U.S. Appl. No. 13/077,374, mailed Feb. 17, 2012.
- Roila et al. 1998, "Prevention of chemotherapy- and radiotherapy-induced emesis: Results of the Perugia consensus conference." *Annals of Oncology*, vol. 9, pp. 811-819.
- USPTO Final Office Action, U.S. Appl. No. 13/077,374, mailed Nov. 23, 2012.
- Piraccini, Gaia et al., *American Society of Clinical Oncology* May 12-15, 2001 San Francisco—USA (vol. 20, part 1 of 2, 2001) (Abstract No. 1595).
- USPTO Non-Final Office Action, U.S. Appl. No. 11/201,035, mailed May 16, 2008.
- USPTO Final Office Action, U.S. Appl. No. 11/201,035, mailed Feb. 4, 2009.
- USPTO Final Office Action, U.S. Appl. No. 11/201,035, mailed Jun. 8, 2010.
- FDA approval letter of Aloxi (palonosetron hydrochloride injection), dated Jul. 25, 2003.
- Macciocchi A, Chernoff SB, Gallagher SC. A phase II dose-ranging study to assess intravenous doses of palonosetron for the prevention of highly emetogenic chemotherapy-induced nausea and vomiting. In: *Program/Proceedings of the 38th Annual Meeting of the American Society of Clinical Oncology*; May 18-21, 2002; Orlando, Fla. Abstract 1480.
- Grunberg SM, Hajdenberg J, Charu V, et al. Palonosetron is active in preventing acute and delayed emesis following moderately emetogenic chemotherapy: results of a phase III trial. *Support Care Cancer* 2002;10:Abstract P-113.
- Aapro MS, Selak E, Lichinitser M, et al. Palonosetron is more effective than ondansetron in preventing chemotherapy-induced nausea and vomiting in patients receiving moderately emetogenic chemotherapy: results of a phase III trial. In: *Program/Proceedings of the 39th Annual Meeting of the American Society of Clinical Oncology*; May 31-Jun. 3, 2003; Chicago, Ill. Abstract 2918.
- Aapro MS, Bertoli L, Lordick F, et al. Palonosetron is effective in preventing acute and delayed chemotherapy induced nausea and vomiting in patients receiving highly emetogenic chemotherapy. *15<sup>th</sup> MASCC International Symposium*, Berlin, Germany. *Support Care Cancer*, vol. 11, No. 6, Jun. 2003, A17.
- Cartmell AD, Ferguson S, Yanagihara R, et al. Protection against chemotherapy-induced nausea and vomiting is maintained over multiple cycles of moderately or highly emetogenic chemotherapy by palonosetron, a potent 5-HT<sub>3</sub> receptor antagonist. In: *Program/Proceedings of the 39th Annual Meeting of the American Society of Clinical Oncology*; May 31-Jun. 3, 2003; Chicago, Ill. Abstract 3041.
- Sabra, Choice of a 5-HT<sub>3</sub> Receptor Antagonist for the Hospital Formulary, *EHP*, Oct. 1996, vol. 2, Supp 1, S19-S24.
- Gregory and Ettinger, 5HT<sub>3</sub> receptor antagonists for the prevention of chemotherapy-induced nausea and vomiting. A comparison of their pharmacology and clinical efficacy. *Drugs*, Feb. 1998; 55(2): 173-189.
- Full Prescribing Information for Aloxi (palonosetron HCl) injection for Intravenous Use (2008).
- Drug, Dose & Schedule Recommendations for Antiemetic Regimens (American Society for Clinical Oncology) (2006).
- Yamakuni, et al., *The Journal of Pharmacology and Experimental Therapeutics*, Probable Involvement of the 5-Hydroxytryptamine<sub>4</sub> Receptor in Methotrexate-Induced Delayed Emesis in Dogs, 2000, *The American Society for Pharmacology and Experimental Therapeutics*, vol. 292, No. 3, p. 1002-1294.
- Geling, et al., Should 5-Hydroxytryptamine-3 Receptor Antagonists Be Administered Beyond 24 Hours After Chemotherapy to Prevent Delayed Emesis? Systematic Re-Evaluation of Clinical Evidence and Drug Cost Implications, *Journal of Clinical Oncology*, vol. 23, No. 6, Feb. 20, 2005 (American Society of Clinical Oncology), pp. 1289-1294.
- Rojas, et al., *International Anesthesia Research Society*,

# 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.