

## (12) United States Patent

Vermeulen et al.

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#### (54) DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS

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#### (56)References Cited

### U.S. PATENT DOCUMENTS

4,804,663	A	2/1989	Kennis et al.
5,158,952	A	10/1992	Janssen et al.
5,254,556	A	10/1993	Janssen et al.
5,453,425	A	9/1995	François et al.
5,612,346	A	3/1997	Mesens et al.
6,077,843	A	6/2000	François et al.
6,555,544	B2	4/2003	François et al.
6,577,545	B2	6/2003	Kim et al.
2002/0082245	A1	6/2002	Yelle
2003/0157180	A1	8/2003	François et al.
2007/0197591	A1	8/2007	Boom et al.
2009/0163519	A1	6/2009	Vermeulen et al.
2011/0105536	A1	5/2011	Lewyn-Briscoe et al.
2012/0263795	A1	10/2012	François et al.

#### FOREIGN PATENT DOCUMENTS

WO	2004/010981	2/2004
WO	WO 2006/114384	11/2006
WO	2008/021342	2/2008
WO	2009/025859	2/2009
WO	2009/047499	4/2009
WO	2009/080651	7/2009
WO	2011/053829	5/2011

#### OTHER PUBLICATIONS

Diagnosed Schizophrenia. Poster No. NR6-21 at the 163rd Annual Meeting of the American Psychiatric Association (APA), New Orleans, Louisiana, USA, May 22-26, 2010.

Alphs L, Haskins, Bossie C, Sliwa JK, Gopal S, Hough D, Davis J Long-term Metabolic Outcomes With Paliperidone Palmitate, A Once-Monthly Long-Acting Injectable Antipsychotic Agent, in the Treatment of Subjects With Schizophrenia. Poster No. 204 at the 48th Annual Meeting of the American College of Neuropsychopharmacology (ACNP), Hollywood, Florida, USA, December 6-10, 2009.

Cleton A, Rossenu S, Crauwels H, Berwaerts J, Hough D, Gopal S, Eerdekens M, Vandebosch A, Rosso Fernandez C Assessment of the Dose Proportionality of Paliperidone Palmitate 25, 50, 100 and 150 mg eq., A New Long-Acting Injectable Antipsychotic, Following Administration in the Deltoid or Gluteal Muscles. Poster at the 2008 Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics (ASCPT), Orlando, Florida, USA, Apr. 2-5, 2008. Coppola D, Liu Y, Gopal S, Remmerie B, Samtani M, Pandina G, Hough D, Nuamah I, Sulaiman A Long-Term Safety, Tolerability and Pharmacokinetics of Paliperidone Palmitate 234 mg (150 mg eq.), The Highest Marketed Dose: A One-Year Open-Label Study in Patients With Schizophrenia. Poster No. PI-49 at the 2010 Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics (ASCPT), Atlanta, Georgia, USA, Mar. 17-20, 2010. Gopal S, Berwaerts J, Nuamah I, Akhras K, Coppola D, Daly E, Hough DW, Palumbo JM Efficacy and Safety of Long-Acting Injectable Paliperidone Palmitate Relative to Long-Acting Haloperidol, Bromperidol and Fluphenazine Decanoate for Long-Term Treatment in Patients With Schizophrenia Using Number Needed to Treat and Number Needed to Harm. Poster at the 65th Annual Convention and Scientific Program of the Society of Biological Psychiatry (SOBP), New Orleans, Louisiana, USA, May 20-22, 2010.

Gopal S, Gassmann-Mayer C, Palumbo J, Samtani MN, Shiwach R, Alphs L, Practical Guidance for Dosing and Switching Paliperidone Palmitate Treatment in Patients with Schizophrenia, Current Medical Research and Opinion 26 (2), p. 377-387, 2010.

Gopal S, Hough DW, Xu H, Lull JM, Gassmann-Mayer C, Remmerie BM, Eerdekens MH, Brown DW, Efficacy and Safety of Paliperidone Palmitate in Adult Patients with Acutely Symptomatic Schizophrenia: A Randomized, Double-Blind, Placebo-Controlled, Dose-Response Study, International Clinical Psychopharmacology, pp. 247-256 (2010).

Gopal S, Lindenmayer JP, Hough D, Melkote R, Lim P, Eerdekens M, Safety and Tolerability of the Investigational Antipsychotic Paliperidone Palmitate Injected in the Deltoid or Gluteus Muscle in Patients with Schizophrenia, 63rd Annual Convention and Scientific Program of the Society of Biological Psychiatry (SOBP), Washington, DC, USA, May 1-3, 2008, Biological Psychiatry 63 (7, Suppl. 7), p. 285S, 2008.

Gopal S, Vijapurkar U, Lim P, Morozova M, Eerdekens M Long-Term Efficacy, Safety and Tolerability of Paliperidone Palmitate in Patients with Schizophrenia. Poster No. 20 at the 12th Annual Meeting of the College of Psychiatric and Neurologic Pharmacists (CPNP), Jacksonville, Florida, Apr. 19-22, 2009.

(Continued)

Primary Examiner — Sreeni Padmanabhan Assistant Examiner - Jody Karol

#### (57)**ABSTRACT**

The present invention provides a method of treating patients in need of treatment with long acting injectable paliperidone palmitate formulations.



#### (56) References Cited

#### OTHER PUBLICATIONS

Haskins JT, Sliwa JK, Ma YW, Pandina GJ, Palumbo J Efficacy and Safety of 234 mg Initation Dose and 3-Fixed Maintenance Doses of Paliperidone Palmitate—A Once-Monthly Injectable Atypical Antipsychotic. Poster No. 123 at the 22nd US Psychiatric and Mental Health Congress (USPMHC), Las Vegas, Nevada, USA, Nov. 2-5, 2009.

Hough D, Gopal S, Vijapurkar U, Lim P, Morozova M, Eerdekens M Paliperidone Palmitate, an Atypical Injectable Antipsychotic, In Prevention of Symptom Recurrence in Patients with Schizophrenia: A Randomized, Double-Blind, Placebo Controlled Study. Poster at the 63rd Annual Convention and Scientific Program of the Society of Biological Psychiatry (SOBP), Washington, DC, USA, May 1-3, 2008

Hough D, Gopal S, Vijapurkar U, Lim P, Morozova M, Eerdekens M, Paliperidone Palmitate in Prevention of Symptom Recurrence in Patients with Schizophrenia: A Randomized, Double-Blind, Placebo-Controlled Study, 161st Meeting of the American Psychiatric Association (APA), Washington, DC, USA, May 3-8, 2008, Proceedings/AbstractBook, p. 173, No. NR4-029, 2008.

Hough D, Lindenmayer JP, Gopal S, Melkote R, Lim P, Herben V, Yuen E, Eerdekens M, Safety and Tolerability of Deltoid and Gluteal Injections of Paliperidone Palmitate in Schizophrenia, Progress in Neuro-Psychopharmacology and Biological Psychiatry 33 (6), p. 1022-1031, 2009.

Kozma C, Dirani R, Nicholl D, Akhras K Evaluation of the Relationships Among Change in Function, Symptoms, and Duration of Schizophrena. Poster No. NR6-4 at the 163rd Annual Meeting of the American Psychiatric Association (APA), New Orleans, Louisiana, USA, May 22-26, 2010.

Kramer M, Litman R, Hough D, Lane R, Lim P, Eerdekens M A 9-Week, Placebo-Controlled Study in Schizophrenia Patients: Efficacy and Safety of the Long-Acting Injectable Agent, Paliperidone Palmitate. Poster No. 4-072 at the 161st Meeting of the American Psychiatric Association (APA), Washington, DC, USA, May 3-8, 2008.

Kramer M, Litman R, Lane R, Lim P, Hough D, Palumbo J, Eerdekens M Efficacy and Tolerability of Two Fixed Dosages of Paliperidone Palmitate in the Treatment of Schizophrenia: Results of a 9-Week Placebo-Controlled Trial. Poster at the 20th US Psychiatric and Mental Health Congress (USPMHC), Orlando, Florida, USA, Oct. 11-14, 2007.

Pandina G, Lane R, Gopal S, Gassmann-Mayer C, Hough D, Remmerie B, Simpson G A Randomized, Double-Blind, Comparative Study of Flexible Doses of Paliperidone Palmitate and Risperidone Long-Acting Therapy in Patients with Schizophrenia. Poster at the 48th Annual Meeting of the American College Neuropsychopharmacology (ACNP), Hollywood, Florida, USA, Dec. 6-10, 2009.

Pandina GJ, Lindenmayer JP, Lull J, Lim P, Gopal S, Kusumakar V, Yuen E, Palumbo J A Randomized, Placebo-Controlled Study to Assess the Efficacy and Safety of Three Doses of Paliperidone Palmitate in Adults with an Acute Exacerbation of Schizophrenia. Poster at the 12th International Congress on Schizophrenia Research (ICOSR), San Diego, California, USA, Mar. 28-Apr. 1, 2009.

Pandina GJ, Lindenmayer JP, Lull J, Lim P, Gopal S, Kusumakar V, Yuen E, Palumbo J A Randomized, Placebo-Controlled Study to Assess the Efficacy and Safety of Three Doses of Paliperidone Palmitate in Adults with an Acute Exacerbation of Schizophrenia. Poster at the 12th Annual Meeting of the College of Psychiatric and Neurologic Pharmacists (CPNP), Jacksonville, Florida, Apr. 19-22, 2009.

Samtani MN, Gopal S, Kern Sliwa J, Haskins JT, Alphs L, Stuyckens K, Vermeulen A Management of Missed Paliperidone Palmitate Doses Based on Pharmacokinetic Modeling and Simulation. Poster at the 49th Annual Meeting of the New Clinical Drug

Samtani MN, Gopal S, Kern Sliwa J, Haskins JT, Alphs L, Stuyckens K, Vermeulen A, Switching to Paliperidone Palmitate From Other Antipsychotics: Guidance Based on Pharmacokinetic Modeling and Simulation, 49th Annual Meeting of the New Clinical Drug Evaluation Unit (NCDEU) of the National Institute of Mental Health (NIMH), Hollywood, Florida, USA, Jun. 29-Jul. 2, 2009, Proceedings/AbstractBook, p. 68, 2009.

Samtani MN, Gopal S, Kern Sliwa J, Haskins T, Alphs L, Stuyckens K, Vermeulen A Paliperidone Palmitate Dosing in Special Patient Populations Including the Elderly and Those With Renal Impairment or Differing Body Mass Index: Guidance Based on Pharmacokinetic Modeling and Simulation. Poster at the American Conference on Pharmacometrics, Mashantucket, Connecticut, USA, Oct. 4-7, 2009.

Samtani MN, Haskins JT, Alphs L, Sliwa JK, Stuyckens K, Herben V, Vermeulen A Maintenance Dosing of Once-Monthly (4-Weekly) Paliperidone Palmitate in Schizophrenia: Pharmacokinetic Rationale Based on Population Simulations. Poster No. 21 at the 12th Annual Meeting of the College of Psychiatric and Neurologic Pharmacists (CPNP), Jacksonville, Florida, Apr. 19-22, 2009.

Samtani MN, Haskins JT, Gopal S, Sliwa JK, Alphs L, Stuyckens K, Vermeulen A Dosing Information for Paliperidone Palmitate—A Once-Monthly Injectable Atypical Antipsychotic—Based on Population Pharmacokinetic Analysis. Poster No. 310 at the 22nd US Psychiatric and Mental Health Congress (USPMHC), Las Vegas, Nevada, USA, Nov. 2-5, 2009.

Samtani MN, Sliwa JK, Haskins JT, Alphs L, Stuyckens K, Herben V, Vermeulen A Initiation Dosing of Deltoid Intramuscular Paliperidone Palmitate in Schizophrenia: Pharmacokinetic Rationale Based on Modeling and Simulation. Poster No. 19 at the 12th Annual Meeting of the College of Psychiatric and Neurologic Pharmacists (CPNP), Jacksonville, Florida, Apr. 19-22, 2009.

Samtani MN, Vermeulen A, Stuyckens K, Population Pharmacokinetics of Intramuscular Paliperidone Palmitate in Patients with Schizophrenia A Novel Once-Monthly, Long-Acting Formulation of an Atypical Antipsychotic, Clinical Pharmacokinetics 48 (9), p. 585-600, 2009.

Sikirica M, Crivera C, Dirani R, Cost-Effectiveness of Paliperidone Palmitate Versus Oral Atypicals in the US. Poster No. NR6-5 at the 163rd Annual Meeting of the American Psychiatric Association (APA), New Orleans, Louisiana, USA, May 22-26, 2010.

Turner N, Bossie CA, Haskins JT, Kern Sliwa J, Ma YW, Alphs L Effects of Paliperidone Palmitate in Acutely ill Subjects With a Marked to Severe Exacerbation of Schizophrenia. Poster No. NR6-26 at the 163rd Annual Meeting of the American Psychiatric Association (APA), New Orleans, Louisiana, USA, May 22-26, 2010.

Alphs et al., "Are the Long-Acting Intramuscular Formulations of Risperidone or Paliperidone Palmitate Associated with Post-Injection Delirium/Sedation Syndrome? An Assessment of Safety Databases", Current Drug Safety, 2011, 6, 43-45.

Alphs et al., "Paliperidone Palmitate Versus Risperidone Long-Acting Therapy in Markedly to Severely ill Subjects With Schizophrenia", Poster presented at the 23rd Annual US Psychiatric and Mental Health Congress; Supported by Ortho-McNeil Janssen Scientific Affairs, LLC Nov. 18-21, 2010; Orlando, FL, USA.

Alphs et al., "Tolerability of Paliperidone Palmitate Initiation Doses in Subjects with Recently Diagnosed Schizophrenia", Poster handout presented at The Scientific Program of XXVII CINP Congress, Hong Kong. Jun. 6-10, 2010.

Alphs et al., "Tolerability of Paliperidone Palmitate Initiation Doses in Subjects with Recently Diagnosed Schizophrenia", Poster presented at The Scientific Program of XXVII CINP Congress, Hong Kong, Jun. 6-10, 2010.

Cleton et al., Clinical Pharmacology & Therapeutics, Mosby-Year Book, St. Louis, MO, US, vol. 81, No. Suppl. 1, p. S63 (2007). Cockcroft et al., Prediction of creatinine clearance from serum creatinine, Nephron, 16:31-41, 1976.

Fleischhacker, W. Wolfgang et al., "A randomized trial of paliperidone palmitate and risperidone long-acting injectable in



#### (56) References Cited

#### OTHER PUBLICATIONS

Gopal et al., "A 52-week open-label study of the safety and tolerability of paliperidone palmitate in patients with schizophrenia", *J Psychopharmacol.* 2010; First View: 1-13.

Gopal et al., "Dosing Information for Paliperidone Palmitate—A Once-Monthly Injectable Atypical Antipsychotic—Based on Population Pharmacokinetic Analysis", Poster presented at The Scientific Program of XXVII CINP Congress, Hong Kong. Jun. 6-10, 2010. Gopal et al., "Efficacy and safety of paliperidone palmitate in adult patients with acutely symptomatic schizophrenia: a randomized, double-blind, placebo-controlled, dose-response study", International Clinical Psychopharmacology 2010, vol. 25 No. 5, pp. 247-256.

Gopal et al., Risk of Cardiovascular Morbidity and Sudden Death with Risperidone and Paliperidone Treatment: Analysis of 64 Randomized, Double-Blind Trials, NR 10-24 Presented at the 164th Annual Meeting—American Psychiatric Association, May 14-18, 2011; Honolulu, Hawaii.

Hough et al., "Paliperidone palmitate maintenance treatment in delaying the time-to-relapse in patients with schizophrenia: A randomized, double-blind, placebo-controlled study", Schizophrenia Research 116 (2010) 107-117.

Hough et al., "Safety and tolerability of deltoid and gluteal injections of paliperidone palmitate in schizophrenia", *Prog Neuropsychopharmacol Biol Psychiatry*. 2009;33:1022-1031.

Li et al., "A Comparative Randomized, Open-label, Rater-blinded Study of Paliperidone Palmitate and Risperidone Long-Acting Injectable Therapy in Patients with Schizophrenia", Poster No. P-11-005 presented at the XXVII CINP Congress, Jun. 6-10, 2010; Hong Kong.

Nasrallah et al., "A Controlled, Evidence-Based Trial of Paliperidone Palmitate, A Long-Acting Injectable Antipsychotic, in Schizophrenia", Neuropsychopharmacology (2010) 35, 2072-2082. Pandina et al., "A double-blind study of paliperidone palmitate and risperidone long-acting injectable in adults with schizophrenia", Progress in Neuro-Psychopharmacology & Biological Psychiatry 2011:35:218-226.

Pandina et al., "A randomized, placebo-controlled study to assess the efficacy and safety of 3 doses of paliperidone palmitate in adults with acutely exacerbated schizophrenia", *J Clin Psychopharmacol.* 2010;30:235-244.

Revill et al., Drugs of the Future, Prous Science, ES, vol. 31, No. 7, pp. 579-584 (2006).

Samtani et al., "Dosing and Switching Strategies for Paliperidone Palmitate", CNS Drugs 2011; 25(10): 829-845.

Samtani et al., "Expansion of Paliperidone Palmitate Day 8 Dose Window from ± 2 Days to ± 4 Days: Model-Based Pharmacokinetic Simulation and Safety Data", Poster presented at the 24th Annual U.S. Psychiatric and Mental Health Congress Meeting, Nov. 7-10, 2011, Las Vegas, Nevada.

Samtani et al., "Expansion of Paliperidone Palmitate Day 8 Dose Window from ± 2 Days to ± 4 Days: Model-Based Pharmacokinetic Simulation and Safety Data", Poster handout presented at the 24th Annual U.S. Psychiatric and Mental Health Congress Meeting, Nov. 7-10, 2011, Las Vegas, Nevada.

Samtani et al., "Switching to Paliperidone Palmitate<sup>1,2</sup> from Other Depot Antipsychotics Guidance Based on Pharmacokinetic Simulations", Population Approach Group in Europe, Applications—CNS (Group IV) Abstr 1839, Berlin, Germany. Jun. 8-11, 2010.

Samtani, Mahesh N., "Use of Model Based Simulations to Support the Paliperidone Palmitate Label", AAPS Workshop on Facilitating Oral Product Development and Reducing Regulatory Burden through Novel Approaches to Assess Bioavailability/Bioequivalence, Oct. 22-23, 2011, Washington.

Sheehan et al., "The Management of Antipsychotic Treatment Discontinuation and Interruptions Using Model-Based Simulations", Poster presented at the 51st Annual NCDEU New Research

Sliwa et al., "Tolerability and Efficacy of Paliperidone Palmitate vs Risperidone Long-acting Injection in Subjects with Recently Diagnosed Schizophrenia", Presented at the 13th International Congress on Schizophrenia Research; Apr. 2-6, 2011; Colorado Springs, Colorado, USA.

Alen et al., Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems,  $8^{th}$  Edition, 2005; pp. 260-263, 652-653, 682.

Guidance Document: Patented Medicines (Notice of Compliance) Regulations, Health Canada, Nov. 12, 2010.

New Drug Application (NDA) dated Oct. 25, 2007 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Invega Sustenna (paliperidone palmitate) 39mg, 78mg, 117mg, 156mg, and 234 mg extended-release injectable suspension, date of letter is Jul. 31, 2009.

Supplemental New Drug Application (sNDA) dated Mar. 14, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Invega Sustenna (paliperidone palmitate) extended-release injectable suspension, 39 mg, 78 mg, 117 mg, 156 mg, and 234 mg.

Alphs et al. Annals of General Psychiatry 2011, 10:12.

Altamura et al., Intramuscular preparations of antipsychotics: uses and relevance in clinical practice. Drugs. 2003; 63(5): 493-512. Berwaerts et al., Journal of Affective Disorders 138 (2012) 247-258. Canuso et al. 2010, Expert Opinion Pharmacother., vol. 11 (15), pp. 2557-2567.

Cleton et al., Assessment of the Dose Proportionality of Paliperidone Palmitate 25, 50, 100 and 150 MG EQ., A New Long-Acting Injectable Antipsychotic Following Administration in the Deltoid or Gluteal Muscles, PI-74, Clinical Pharmacology & Therapeutics, vol. 83, Supplement 1, Mar. 2008, S31.

Ereshefsky L., Pharmacokinetics and drug interactions: update for new antipsychotics. J Clin Psychiatry. 1996;57 Suppl 11:12-25. Gefvert et al. Pharmacokinetics and D2 receptor occupancy of long-acting injectable risperidone (Risperdal Consta) in patients with schizophrenia. Int J Neuropsychopharmacol. 2005; 8(1): 27-36.

Kane et al., Guidelines for depot antipsychotic treatment in schizophrenia. European Neuropsychopharmacology Consensus Conference in Siena, Italy. Eur Neuropsychopharmacol. 1998; 8(1): 55-66. Levron et al., Clinical pharmacokinetics of haloperidol decanoate. Comparison with other prolonged-action neuroleptics. Encephale. 1987; 13(2): 83-7 [see English Summary as provided].

Markowitz et al., "Benefit-Risk Assessment of Maintenance Therapy in Schizophrenia Comparing Long-Acting Injectable (LAI) Paliperidone Palmitate with Paliperidone ER", Presented at the 164th Annual Meeting of the American Psychiatric Association, May 14-18, 2011, Honolulu, HI, USA.

Mauri et al., Clinical pharmacokinetics of atypical antipsychotics: a critical review of the relationship between plasma concentrations and clinical response. Clin Pharmacokinet. 2007;46(5):359-88.

Pandina et al., Progress in Neuro-Psychopharmacology & Biological Psychiatry 35 (2011) 218-226.

Sheehan et al., Comparison of the Peak-to-trough Fluctuation in Plasma Concentration of Long-acting Injectable Antipsychotics and Their Oral Equivalents, *Innov Clin Neurosci.* 2012;9(7-8):17-23.

Vermeir et al., Absorption, metabolism, and excretion of paliperidone, a new monoaminergic antagonist, in humans. Drug Metab Dispos. Apr. 2008;36(4):769-79.

Lewyn-Briscoe et al., U.S. Appl. No. 13/903,638.

Pharmacists, Inc. (2007), pp. 103-108.

International Search Report Re: International Application No. PCT/US2010/054807 dated Jan. 11, 2011.

Office Action mailed Feb. 28, 2013 in U.S. Appl. No. 12/916,910. Kazuo Yamada et al., Future Potentiality of Pharmacotherapy for Schizophrenia in Acute Phase, Clinical Psychopharmacology, vo. 8, No. 10 (2005), pp. 1563-1568.

Takashi Yoshio, Sustained-release Antipsychotic Drugs (depot drugs), Psychiatric Nursing, vol. 33, No. 4 (2006), pp. 64-67. Gibaldi's Drug Delivery Systems in Pharmaceutical Care. edited by Mary Lee, Archana Desai, American Society of Health-System



#### (56) References Cited

#### OTHER PUBLICATIONS

Australian Patent Opposition for AU Patent Appl No. 2008340101 dated May 20, 2015.

Statement of Grounds and Particulars dated Aug. 19, 2015 re: Australian Patent Opposition for AU Patent Appl No. 2008340101. Cleton A, Rossenu S, Crauwels H, et al. A single-dose, open-label, parallel, randomized, dose-proportionality study of paliperidone after intramuscular injections of paliperidone palmitate in the deltoid or gluteal muscle in patients with schizophrenia. *J Clin Pharmacol.* 2014;54(9):1048-1057.

Cleton A, Rossenu S, Hough D, Crauwels H, Vandebosch A, Berwaerts J, Eerdekens M, Francetic, I. "Evaluation of the pharmacokinetic profile of gluteal versus deltoid intramuscular Injections of paliperidone palmitate 100 mg equivalent in patients with schizophrenia" *Clin.Pharmacal. Therapeutics*. Published Mar. 2008.

Cockshott WP, Thompson GT, Howlett LJ, Seeley ET. Intramuscular or intralipomatous injections? *N Engl J Med.* 1982;307(6):356-358.

Haramati N, Lorans R, Lutwin M, Kaleya RN. Injection granulomas. Intramuscle or intrafat? *Arch Fam Med.* 1994;3(2):146-148. Janicak, P. G. and Winans, E. A. "Paliperidone ER: a review of the clinical trial data" *Neuropsychiatr. Dis. Treat.* Dec. 3, 2007(6): 869-897 Published Jan. 15, 2008.

Rosen, H, and Abribat, T. "The rise and rise of drug delivery" Nat. Rev. Drug Discov. May 4, 2005(5): 381-5.

Rossenu S, Cleton A, Hough D, et al. Pharmacokinetic profile after multiple deltoid or gluteal intramuscular injections of paliperidone palmitate in patients with schizophrenia. *Clinical Pharmacology in Drug Development*. 2015;4(4):270-278.

Samtani MN, Vermeulen A, Stuyckens K. Population pharmacokinetics of intramuscular paliperidone palmitate in patients with schizophrenia: a novel once-monthly, long-acting formulation of an atypical antipsychotic. *Clin Pharmacokinet*. 2009;48(9):585-600.

Synopsis of the Phase III clinical study described at Example 8 of the opposed application accessed at http://yoda.yale.edu/sites/default/files/nct00590577.pdf on Aug. 17, 2015, Issue Date: Sep. 12, 2008

Yin J, Collier AC, Barr AM, Honer WG, Procyshyn RM. Paliperidone Palmitate Long-Acting Injectable Given Intramuscularly in the Deltoid Versus the Gluteal Muscle: Are They Therapeutically Equivalent? *J Clin Psychopharmacol.* 2015;35(4):447-449.

Kreyenbuhi, et al., "Adding or Switching Antipsychotic Medications in Treatment-Refractory Schizophrenia", Psychiatr Serv., Jul. 2007, pp. 983-990, vol. 58(7).

Third Party Observations dated Jan. 28, 2016 filed during prosecution of EP Application No. 10773821.3.

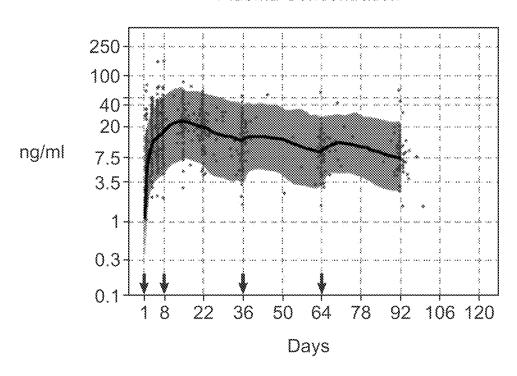
Office Action mailed Mar. 24, 2015 in U.S. Appl. No. 13/903,638. Final Office Action mailed Oct. 22, 2015 in U.S. Appl. No. 13/903,638.

Cirincione, et al., "Population pharmacokinetics of paliperidone ER in healthy subjects and patients with schizophrenia", clinical Pharmacology & Therapeutics, vol. 81, Issue Supplement SI, P. S19 (published in Mar. 2007).



FIG. 1

## Plasma Concentration





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