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- (54) **METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS**
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CPC **A61K 47/02** (2013.01); **A61K 9/0048** (2013.01); **A61K 9/107** (2013.01); **A61K 38/13** (2013.01); **A61K 47/10** (2013.01); **A61K 47/22** (2013.01); **A61K 47/32** (2013.01); **A61K 47/44** (2013.01)
- (58) **Field of Classification Search**
None
See application file for complete search history.
- (56) **References Cited**

U.S. PATENT DOCUMENTS

3,278,447 A 10/1966 McNicholas
4,347,238 A 8/1982 Hollingsbee4,388,307 A 6/1983 Cavanak
4,614,736 A 9/1986 Devallee et al.
4,649,047 A 3/1987 Kaswan
4,764,503 A 8/1988 Wenger
4,814,323 A 3/1989 Andrieu et al.
4,839,342 A 6/1989 Kaswan
4,970,076 A 11/1990 Horrobin
4,990,337 A 2/1991 Kurihara et al.
4,996,193 A 2/1991 Hewitt et al.
5,011,681 A 4/1991 Ciotti et al.
5,047,396 A 9/1991 Orban et al.
5,051,402 A 9/1991 Kurihara et al.
5,053,000 A 10/1991 Booth et al.
5,075,104 A 12/1991 Gressel et al.
5,286,730 A 2/1994 Caufield et al.
5,286,731 A 2/1994 Caufield et al.
5,294,604 A 3/1994 Nussenblatt et al.
5,296,158 A 3/1994 MacGilp et al.
5,342,625 A 8/1994 Hauer et al.
5,364,632 A 11/1994 Benita et al.
5,368,854 A 11/1994 Rennick
5,411,952 A 5/1995 Kaswan
5,424,078 A 6/1995 Dziabo
5,441,732 A 8/1995 Hoeg et al.
5,474,919 A 12/1995 Chartrain et al.
5,474,979 A 12/1995 Ding et al.
5,496,811 A 3/1996 Aviv et al.
5,504,068 A 4/1996 Komiya et al.
5,540,931 A 7/1996 Hewitt et al.
5,543,393 A 8/1996 Kim et al.
5,578,586 A 11/1996 Glonek et al.

(Continued)

FOREIGN PATENT DOCUMENTS

DE 19810655 9/1999
EP 0448856 10/1991

(Continued)

OTHER PUBLICATIONS

Abdulrazik, M. et al, Ocular Delivery of Cyclosporin A II. Effect of Submicron Emulsion's Surface Charge on Ocular Distribution of Topical Cyclosporin A, S.T.P. Pharma Sciences, Dec. 2001, 427-432, 11(6).

(Continued)

Primary Examiner — Marcela M Cordero Garcia(74) *Attorney, Agent, or Firm* — Laura L. Wine; Joel B. German; Debra D. Condino(57) **ABSTRACT**

Methods of treating an eye of a human or animal include administering to an eye of a human or animal a composition in the form of an emulsion including water, a hydrophobic component and a cyclosporin component in a therapeutically effective amount of less than 0.1% by weight of the composition. The weight ratio of the cyclosporin component to the hydrophobic component is less than 0.8.

(56)

References Cited

U.S. PATENT DOCUMENTS

5,589,455 A 12/1996 Woo
 5,591,971 A 1/1997 Shahar et al.
 5,614,491 A 3/1997 Walch et al.
 5,639,724 A 6/1997 Cavanak
 5,652,212 A 7/1997 Cavanak et al.
 5,719,123 A 2/1998 Morley et al.
 5,721,273 A 2/1998 Sallee et al.
 5,739,105 A 4/1998 Kim et al.
 5,753,166 A 5/1998 Dalton et al.
 5,766,629 A 6/1998 Cho et al.
 5,798,333 A 8/1998 Sherman
 5,807,820 A 9/1998 Elias
 5,827,822 A 10/1998 Floc'h et al.
 5,827,862 A 10/1998 Yamamura
 5,834,017 A 11/1998 Cho et al.
 5,843,452 A 12/1998 Wiedmann et al.
 5,843,891 A 12/1998 Sherman
 5,858,401 A 1/1999 Bhalani et al.
 5,866,159 A 2/1999 Hauer et al.
 5,891,846 A 4/1999 Ishida et al.
 5,916,589 A 6/1999 Hauer et al.
 5,929,030 A 7/1999 Hamied et al.
 5,951,971 A 9/1999 Kawashima et al.
 5,962,014 A 10/1999 Hauer et al.
 5,962,017 A 10/1999 Hauer et al.
 5,962,019 A 10/1999 Cho et al.
 5,977,066 A 11/1999 Cavanak
 5,981,479 A 11/1999 Ko et al.
 5,981,607 A 11/1999 Ding et al.
 5,998,365 A 12/1999 Sherman
 6,004,566 A 12/1999 Friedman et al.
 6,007,840 A 12/1999 Hauer et al.
 6,008,191 A 12/1999 Singh
 6,008,192 A 12/1999 Al-Razzak et al.
 6,022,852 A 2/2000 Klokkers et al.
 6,024,978 A 2/2000 Hauer et al.
 6,046,163 A 4/2000 Stuchlik et al.
 6,057,289 A 5/2000 Mulye
 6,159,933 A 12/2000 Sherman
 6,197,335 B1 3/2001 Sherman
 6,254,860 B1 7/2001 Garst
 6,254,885 B1 7/2001 Cho et al.
 6,267,985 B1 7/2001 Chen et al.
 6,284,268 B1 9/2001 Mishra et al.
 6,294,192 B1 9/2001 Patel et al.
 6,306,825 B1 10/2001 Cavanak
 6,323,204 B1 11/2001 Burke
 6,346,511 B1 2/2002 Singh et al.
 6,350,442 B2 2/2002 Garst
 6,413,547 B1 7/2002 Bennett et al.
 6,420,355 B2 7/2002 Richter et al.
 6,468,968 B2 10/2002 Cavanak et al.
 6,475,519 B1 11/2002 Meinzer et al.
 6,486,124 B2 11/2002 Olbrich et al.
 6,544,953 B2 4/2003 Tsuzuki et al.
 6,555,526 B2 4/2003 Matsuo et al.
 6,562,873 B2 5/2003 Olejnik et al.
 6,569,463 B2 5/2003 Patel et al.
 6,582,718 B2 6/2003 Kawashima
 6,656,460 B2 12/2003 Benita et al.
 6,872,705 B2 3/2005 Lyons
 6,984,628 B2 1/2006 Bakhit et al.
 7,202,209 B2 4/2007 Chang
 7,276,476 B2 10/2007 Chang et al.
 7,288,520 B2 10/2007 Chang et al.
 7,297,679 B2 11/2007 Chang
 7,501,393 B2 3/2009 Tien et al.
 8,211,855 B2 7/2012 Chang et al.
 8,288,348 B2 10/2012 Chang et al.
 8,618,064 B2 12/2013 Acheampong et al.
 8,629,111 B2 1/2014 Acheampong et al.
 8,633,162 B2 1/2014 Acheampong et al.
 8,642,556 B2 2/2014 Acheampong et al.
 8,648,048 B2 2/2014 Acheampong et al.

9,101,574 B2* 8/2015 Chang A61K 9/0048
 2001/0003589 A1 6/2001 Neuer et al.
 2001/0014665 A1 8/2001 Fischer et al.
 2001/0036449 A1 11/2001 Garst
 2002/0012680 A1 1/2002 Patel et al.
 2002/0013272 A1 1/2002 Cavanak et al.
 2002/0016290 A1 2/2002 Floc'h et al.
 2002/0016292 A1 2/2002 Richter et al.
 2002/0025927 A1 2/2002 Olbrich et al.
 2002/0045601 A1 4/2002 Kawashima
 2002/0107183 A1 8/2002 Petszulat et al.
 2002/0119190 A1 8/2002 Meinzer et al.
 2002/0165134 A1 11/2002 Richter et al.
 2003/0021816 A1 1/2003 Kang et al.
 2003/0044452 A1 3/2003 Ueno
 2003/0055028 A1 3/2003 Stergiopoulos et al.
 2003/0059470 A1 3/2003 Muller
 2003/0060402 A1 3/2003 Cavanak et al.
 2003/0087813 A1 5/2003 Or et al.
 2003/0104992 A1 6/2003 Or et al.
 2003/0108626 A1 6/2003 Benita et al.
 2003/0109425 A1 6/2003 Or et al.
 2003/0109426 A1 6/2003 Or et al.
 2003/0133984 A1 7/2003 Ambuhl et al.
 2003/0143250 A1 7/2003 Hauer et al.
 2003/0147954 A1 8/2003 Yang et al.
 2003/0166517 A1 9/2003 Fricker et al.
 2005/0014691 A1 1/2005 Bakhit et al.
 2005/0059583 A1 3/2005 Acheampong
 2007/0015691 A1 1/2007 Chang
 2007/0027072 A1 2/2007 Tien et al.
 2007/0087962 A1 4/2007 Tien et al.
 2007/0149447 A1 6/2007 Chang et al.
 2008/0039378 A1 2/2008 Graham et al.
 2008/0070834 A1 3/2008 Chang et al.
 2008/0146497 A1 6/2008 Graham et al.
 2008/0207495 A1 8/2008 Graham et al.
 2009/0131307 A1 5/2009 Tien et al.
 2010/0279951 A1 11/2010 Morgan et al.
 2011/0009339 A1 1/2011 Schiffman
 2011/0294744 A1 12/2011 Morgan et al.
 2012/0270805 A1 10/2012 Chang et al.
 2013/0059796 A1 3/2013 Chang et al.

FOREIGN PATENT DOCUMENTS

EP 0471293 2/1992
 EP 0480690 4/1992
 EP 0547229 1/1993
 EP 0760237 3/1997
 GB 2222770 A 3/1990
 JP 0558906 A 3/1993
 WO 8901772 A1 3/1989
 WO 9318752 A1 9/1993
 WO 1995-031211 11/1995
 WO 00-00179 1/2000
 WO 01-32142 5/2001
 WO 01-41671 6/2001
 WO 02-09667 2/2002
 WO 02-49603 6/2002
 WO 03-030834 4/2003
 WO 03-053405 7/2003

OTHER PUBLICATIONS

Acheampong, Andrew et al, Cyclosporine Distribution into the Conjunctiva, Cornea, Lacrimal Gland and Systemic Blood Following Topical Dosing of Cyclosporine to Rabbit, Dog and Human eyes, 1996, 179.

Acheampong, Andrew et al, Cyclosporine Distribution Into the Conjunctiva, Cornea, Lacrimal Gland, and Systemic Blood Following Topical Dosing of Cyclosporine to Rabbit, Dog, and Human Eyes, Adv. Exp. Med. Biol., 1998, 1001-1004, 438.

Acheampong, Andrew et al, Distribution of Cyclosporin a in Ocular Tissues After Topical Administration to Albino Rabbits and Beagle

(56)

References Cited

OTHER PUBLICATIONS

- Akpek, Esen Karamursel et al, A Randomized Trial of Topical Cyclosporin 0.05% in Topical Steroid-Resistant Atopic Keratoconjunctivitis, *Ophthalmology*, 2004, 476-482, 111.
- Angelov, O. et al, Preclinical Safety Studies of Cyclosporine Ophthalmic Emulsion, *Adv Exp Med Biol*, 1998, 991-995, 438.
- Angelov, O. et al, Safety Assessment of Cyclosporine Ophthalmic Emulsion in Rabbits and Dogs, XIth Congress of the European Society of Ophthalmology, 1997, 25-28, 1-5, Soc. Ophthalmol Eur., HU.
- Ardizzone, Sandro et al, A Practical Guide to the Management of Distal Ulcerative Colitis, *Drugs*, 1998, 519-542, 55(4).
- Banic, Marko et al, Effect of Cyclosporine in a Murine Model of Experimental Colitis, *Digestive Diseases and Sciences*, Jun. 2002, 1362-1368, 47(6).
- BF Goodrich, Carbopol 1342 A New Polymer Which Functions Both As a Thickener and an Emulsifier TDS-73, Carbopol High Performance Polymers, 1987, 25 Pages.
- BF Goodrich, Carbopol, Pemulen and Noveon Polymers, 1995, 2 Pages.
- BF Goodrich, Pemulen Polymeric Emulsifiers TDS-182, Mar. 1993, 9 Pages.
- Bonini, S. et al, Vernal Keratoconjunctivitis, *Eye*, 2004, 345-351, 18.
- Brewster, Marcus et al, Enhanced Delivery of Ganciclovir to the Brain Through the Use of Redox Targeting, *Antimicrobial Agents and Chemotherapy*, Apr. 1994, 817-823, 38(4).
- Brewster, Marcus et al, Intravenous and Oral Pharmacokinetic Evaluation of a 2-Hydroxypropyl- β -cyclodextrin-Based Formulation of Carbamazepine in the Dog: Comparison with Commercially Available Tablets and Suspensions, *Journal of Pharmaceutical Sciences*, Mar. 1997, 335-339, 86(3).
- Brewster, Marcus et al, Preparation, Characterization, and Anesthetic Properties of 2-Hydroxypropyl- β -cyclodextrin Complexes of Pregnanolone and Pregnenolone in Rat and Mouse, *Journal of Pharmaceutical Sciences*, Oct. 1995, 1154-1159, 84(10).
- Brinkmeier, Thomas et al, Pyodermitis-Pyostomatitis Vegetans: A Clinical Course of Two Decades with Response to Cyclosporine and Low-Dose Prednisolone, *Acta Derm Venereol*, 2001, 134-136, 81.
- Castillo, Jose M. Benitez Del et al, Influence of Topical Cyclosporine A and Dissolvent on Corneal Epithelium Permeability of Fluorescein, *Documenta Ophthalmologica*, 1995, 49-55, 91.
- Cheeks, Lisa et al, Influence of Vehicle and Anterior Chamber Protein Concentration on Cyclosporine Penetration Through the Isolated Rabbit Cornea, *Current Eye Research*, 1992, 641-649, 11(7).
- Database WPI Week 200044, Derwent Pub. Ltd., London, GB; An 2000-492678 & JP2000/143542, 2000, 2 Pages.
- Ding, Shulin et al, Cyclosporine Ophthalmic O/W Emulsion: Formulation and Emulsion Characterization, *Pharm Res*, 1997, 1 page, 14 (11).
- Donnenfeld, Eric D., The Economics of Using Restasis, *Ophthalmology Management*, Oct. 2003, 3 pages, US.
- Drosos, A. A. et al, Efficacy and Safety of Cyclosporine-A Therapy for Primary Sjogren's Syndrome, *Ter. Arkh.*, 1998, 77-80, 60(4).
- Drosos, A.A. et al, Cyclosporin a Therapy in Patients with Primary Sjogren's Syndrome: Results at One Year, *Scand J Rheumatology*, 1986, 246-249, 61.
- Durrani, A.M. et al, Pilocarpine Bioavailability From a Mucoadhesive Liposomal Ophthalmic Drug Delivery System, *International Journal of Pharmaceutics*, 1992, 409-415, 88.
- Eisen, Drore et al, Topical Cyclosporine for Oral Mucosal Disorders, *J Am Acad Dermatol*, Dec. 1990, 1259-1264, 23.
- Epstein, Joel et al, Topical Cyclosporine in a Bioadhesive for Treatment of Oral Lichenoid Mucosal Reactions, *Oral Surg Oral Med Oral Pathol Oral*, 1996, 532-536, 82.
- Erdmann, S. et al, Pemphigus Vulgaris Der Mund—Und Kehlkopfschleimhaut Pemphigus Vulgaris of the Oral Mucosa and the Larynx, *H+G Zeitschrift Fuer Hautkrankheiten*, 1997, 283-286, 72(4).
- FDA Concludes Restasis (Cyclosporine) Not Effective for Dry Eye (Jun. 18, 1999). Accessed online at <http://www.dryeyeinfo.org/>
- Gaeta, G.M. et al, Cyclosporin Bioadhesive Gel in the Topical Treatment of Erosive Oral Lichen Planus, *International Journal of Immunopathology and Pharmacology*, 1994, 125-132, 7(2).
- Gipson, Ilene et al, Character of Ocular Surface Mucins and Their Alteration in Dry Eye Disease, *The Ocular Surface*, Apr. 2004, 131-148, 2(2).
- Gremse, David et al, Ulcerative Colitis in Children, *Pediatr Drugs*, 2002, 807-815, 4(12).
- Gunduz, Kaan et al, Topical Cyclosporin Treatment of Keratoconjunctivitis Sicca in Secondary Sjogren's Syndrome, *Acta Ophthalmologica*, 1994, 438-442, 72.
- <http://web.archive.org/web/2001030625323/http://www.surfactant.co.kr/surfactants/pegester.html>, 2001, 6 Pages, retrieved on Jul. 5, 2008.
- Hunter, P.A. et al, Cyclosporin A Applied Topically to the Recipient Eye Inhibits Corneal Graft Rejection, *Clin Exp Immunol*, 1981, 173-177, 45.
- Jumaa, Muhannad et al, Physicochemical Properties and Hemolytic Effect of Different Lipid Emulsion Formulations Using a Mixture of Emulsifiers, *Pharmaceutica Acta Helvetica*, 1999, 293-301, 73.
- Kanai, A. et al, The Effect on the Cornea of Alpha Cyclodextrin Vehicle for Eye Drops, *Transplantation Proceedings*, Feb. 1989, 3150-3152, vol. 21.
- Kanpolat, Ayfer et al, Penetration of Cyclosporin a into the Rabbit Cornea and Aqueous Humor after Topical Drop and Collagen Shield Administration, *Cornea/External Disease*, Apr. 1994, 119-122, 20(2).
- Kaur, Rabinder et al, Solid Dispersions of Drugs in Polyocethylene 40 Stearate: Dissolution Rates and Physicochemical Interactions, *Journal of Pharmacy and Pharmacology*, Dec. 1979, 48P.
- Kuwano, Mitsuaki et al, Cyclosporine A Formulation Affects Its Ocular Distribution in Rabbits, *Pharmaceutical Research*, Jan. 2002, 108-111, 19(1).
- Lambert Technologies Corp. Material Safety Data Sheet for LUMULSE™ POE-40 MS KP, last revision Aug. 22, 2003. 3 pages.
- Leibovitz, Z. et al., Our Experience in Processing Maize (Corn) Germ Oil, *Journal of the American Oil Chemists Society*, Feb. 1983, 395-399, 80 (2), US.
- Lixin, Xie et al, Effect of Cyclosporine a Delivery System in Corneal Transplantation, *Chinese Medical Journal*, 2002, 110-113, 115 (1), US.
- Lopatin, D.E., Chemical Compositions and Functions of Saliva, Aug. 24, 2001, 31 Pages.
- Lyons, R.T. et al, Influence of Three Emulsion Formulation Parameters on the Ocular Bioavailability of Cyclosporine A in Albino Rabbits, *Am Assoc Pharm Sci*, 2000, 1 Page, 2(4).
- Pedersen, Anne Marie et al, Primary Sjogren's Syndrome: Oral Aspects on Pathogenesis, Diagnostic Criteria, Clinical Features and Approaches for Therapy, *Expert Opin Pharma*, 2001, 1415-1436, 2(9).
- Phillips, Thomas et al, Cyclosporine Has a Direct Effect on the Differentiation of a Mucin-Secreting Cell Line, *Journal of Cellular Physiology*, 2000, 400-408, 184.
- Present, D.H. et al, Cyclosporine and Other Immunosuppressive Agents: Current and Future Role in the Treatment of Inflammatory Bowel Disease, *American Journal of Gastroenterology*, 1993, 627-630, 88(5).
- Restasis® Product Information Sheet, Allergan, Inc., 2009, 5 Pages.
- Restasis® Increasing Tear Production, Retrieved on Aug. 14, 2009, http://www.restasisprofessional.com/_clinical/clinical_increasing.htm 3 pages.
- Robinson, N. A. et al, Desquamative Gingivitis: A Sign of Mucocutaneous Disorders—a Review, *Australian Dental Journal*, 2003, 205-211, 48(4).
- Rudinger, J., Characteristics of the Amino Acids as Components of a Peptide Hormone Sequence, *Peptide Hormones*, 1976, 1-7.
- Sall, Kenneth et al, Two Multicenter, Randomized Studies of the Efficacy and Safety of Cyclosporine Ophthalmic Emulsion in Moderate to Severe Dry Eye Disease, *Ophthalmology*, 2000, 631-639, 107.
- Sandborn, William et al, A Placebo-Controlled Trial of Cyclosporine Enemas for Mildly to Moderately Active Left-Sided Ulcerative

(56)

References Cited

OTHER PUBLICATIONS

- Sandborn, William et al, Cyclosporine Enemas for Treatment-Resistant, Mildly to Moderately Active, Left-Sided Ulcerative Colitis, *American Journal of Gastroenterology*, 1993, 640-645, 88(5).
- Schwab, Matthias et al, Pharmacokinetic Considerations in the Treatment of Inflammatory Bowel Disease, *Clin Pharm*, 2001, 723-751, 60(10).
- Secchi, Antonio et al, Topical Use of Cyclosporine in the Treatment of Vernal Keratoconjunctivitis, *American Journal of Ophthalmology*, Dec. 1990, 641-645, 110.
- Small, Dave et al, The Ocular Pharmacokinetics of Cyclosporine in Albino Rabbits and Beagle Dogs, *Ocular Drug Delivery and Metabolism*, 1999, 54.
- Small, David et al, Blood Concentrations of Cyclosporin a During Long-Term Treatment With Cyclosporin A Ophthalmic Emulsions in Patients with Moderate to Severe Dry Eye Disease, *Journal of Ocular Pharmacology and Therapeutics*, 2002, 411-418, 18(5).
- Smilek, Dawn et al, A Single Amino Acid Change in a Myelin Basic Protein Peptide Confers the Capacity to Prevent Rather Than Induce Experimental Autoimmune Encephalomyelitis, *Proc. Natl. Acad. Sci.*, Nov. 1991, 9633-9637, 88.
- Stephenson, Michelle, The Latest Uses of Restasis, Review of *Ophthalmology*, Dec. 30, 2005, 7 Pages, US.
- Stevenson, Dara et al, Efficacy and Safety of Cyclosporin A Ophthalmic Emulsion in the Treatment of Moderate-to-Severe Dry Eye Disease, *Ophthalmology*, 2000, 967-974, 107.
- Tesavibul, N. et al, Topical Cyclosporine A (CsA) for Ocular Surface Abnormalities in Graft Versus Host Disease Patients, *Invest Ophthalmol Vis Sci*, Feb. 1996, S1026, 37(3).
- The Online Medical Dictionary, Derivative, Analog, Analogue, Xerostomia, accessed Jul. 7, 2005 and Jul. 13, 2005, 6 Pages.
- The United States Pharmacopeia, USP XXII, Jan. 1990, 8 Pages, 22.
- Tibell, A. et al., Cyclosporin A in Fat Emulsion Carriers: Experimental Studies on Pharmacokinetics and Tissue Distribution, *Pharmacology & Toxicology*, 1995, 115-121, 76, US.
- Tsubota, Kazuo et al, Use of Topical Cyclosporin a in a Primary Sjogren's Syndrome Mouse Model, *Invest Ophthalmol Vis Sci*, Aug. 1998, 1551-1559, 39(9).
- Van Der Reijden, Willy et al, Treatment of Oral Dryness Related Complaints (Xerostomia) in Sjogren's Syndrome, *Ann Rheum Dis*, 1999, 465-473, 58.
- Wiederholt, Michael et al, Pharmacokinetic of Topical Cyclosporin A in the Rabbit Eye, *Invest Ophthalmol Vis Sci*, 1986, 519-524, 27.
- Winter, T.A. et al, Cyclosporin A Retention Enemas in Refractory Distal Ulcerative Colitis and 'Pouchitis', *Scand J Gastroenterol*, 1993, 701-704, 28.
- Pending U.S. Appl. No. 13/961,828 and its entire prosecution history, filed Aug. 7, 2013.
- U.S. Appl. No. 90/009,944 and its entire prosecution history, filed Aug. 27, 2011.
- Albietz, Julie, Dry Eye: An Update on Clinical Diagnosis, Management and Promising New Treatments, *Clin & Exp. Optometry*, Apr. 18, 2001, 84.
- Allergan Dry Eye Product Portfolio Fact Sheet (http://www.allergan.com/assets/pdf/dry_eye_product_portfolio_fact_sheet.pdf), 4 Pages, 2015.
- Allergan, Inc. 2001 Annual Report, Downloaded from <http://agn.client.shareholder.com/financials.cfm>, last accessed Jan. 1, 2015, 54 Pages.
- Allergan, Inc. 2002 Annual Report (<http://agn.client.shareholder.com/financials.cfm>), 52 Pages, 2015.
- Allergan, Inc. 2003 Annual Report, Downloaded from <http://agn.client.shareholder.com/financials.cfm>, last accessed Jan. 1, 2015, 52 Pages.
- Allergan, Inc. 2004 Annual Report, Downloaded from <http://agn.client.shareholder.com/financials.cfm>, last accessed Jan. 1, 2015, 16 Pages.
- Allergan, Inc. 2006 Annual Report, Downloaded from <http://agn.client.shareholder.com/financials.cfm>, last accessed Jan. 1, 2015, 18 Pages.
- Allergan, Inc. 2005 Annual Report, Downloaded from <http://agn.client.shareholder.com/financials.cfm>, last accessed Jan. 1, 2015, 35 Pages.
- Allergan, Inc. 2009 Annual Report, Downloaded from <http://agn.client.shareholder.com/financials.cfm>, last accessed Jan. 1, 2015, 18 Pages.
- Allergan, Inc. 2010 Annual Report, Downloaded from <http://agn.client.shareholder.com/financials.cfm>, last accessed Jan. 1, 2015, 206 Pages.
- Allegran, Inc. 2011 Annual Report, Downloaded from <http://agn.client.shareholder.com/financials.cfm>, last accessed Jan. 1, 2015, 174 Pages.
- Allergan, Inc. 2012 Annual Report, Downloaded from <http://agn.client.shareholder.com/financials.cfm>, last accessed Jan. 1, 2015, 28 Pages.
- Allergan, Inc. 2013 Annual Report, Downloaded from <http://agn.client.shareholder.com/financials.cfm>, last accessed Jan. 1, 2015, 28 Pages.
- American Academy of Ophthalmology Cornea/External Disease Panel. Preferred Practice Pattern Guidelines. Dry Eye Syndrome. San Francisco, CA: American Academy of Ophthalmology, 2013, 44 Pages.
- Autry, Jill et al, Mix It Up: When to Call a Compounding Pharmacist, *Review of Optometry*, Jul. 15, 2012, 30-37, 149.
- Bausch and Lomb "Dry Eye Products," downloaded from Bausch and Lomb Website <http://www.bausch.com/our-products/dry-eye-products/dry-eye-products>, last accessed Apr. 14, 2015, 2 Pages.
- Certain Ophthalmic Combination Drugs Containing a Steroid and Anti-Infective(s) for Human Use; Drug Efficacy Study Implementation; Amendment, Federal Register, 1982, 21296-21301, 47.
- Certain Steroid Preparations for Ophthalmic and/or Otic Use, Federal Register, 1976, 34340-34342, 41.
- Chanana, Gurmukh et al, Particle Size Reduction of Emulsions by Formulation Design-II: Effect of Oil and Surfactant Concentration, *PDA Journal of Pharmaceutical Science and Technology*, 1995, 71-76, 49(2).
- Chidambaram, N. et al, Effect of Nonionic Surfactant on Transport of Surface-Active and Non-Surface-Active Model Drugs and Emulsion Stability in Triphasic Systems, *AAPS PharmSci*, 2000, 1-11, 2(3).
- Chung, Hesson et al, Oil Components Modulate Physical Characteristics and Function of the Natural Oil Emulsions As Drug or Gene Delivery System, *Journal of Controlled Release*, 2001, 339-350, 71.
- Coles, William et al, Dynamics of Ocular Surface pH, *British Journal of Ophthalmology*, 1984, 549-552, 68.
- CTFA Becomes the Personal Care Products Council, 1 Page, 2015 (<http://www.personalcarecouncil.org/ctfa-becomes-personal-care-products-council>).
- Curriculum Vitae of Christopher N. Ta, Ph.D., 23 Pages, 2015.
- Curriculum Vitae of Erning Xia, Ph.D., 17 Pages, 2015.
- Curriculum Vitae of Harry C. Boghigian, 11 Pages, 2015.
- De Paiva, C.S. et al, Rationale for Anti-Inflammatory Therapy in Dry Eye Syndrome, *Arq. Bras. Oftalmol.*, 2008, 89-95, 71.
- Declaration of Christopher N. Ta, Ph.D., 57 Pages, 2015.
- Declaration of Erning Xia, Ph.D., 197 Pages, 2015.
- Declaration of Harry C. Boghigian, 37 Pages, 2015.
- Drugs@FDA: FDA Approved Drug Products, Lacrisert, downloaded from the FDA website <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails>, last accessed Apr. 16, 2015, 2 Pages.
- Drugs@FDA: FDA Approved Drug Products, Restasis, downloaded from the FDA website <http://www.accessdata.fda.gov/scripts/cder/ob/docs/temptn.cfm>, last accessed Apr. 14, 2015, 2 Pages.
- Dry Eye Drop Symptom Relief Product information at Systane.com, Systane products, Systane ultra Lubricant Eye Drops, downloaded from Alcon website <http://www.systane.com/Dry-Eye-Drop.aspx>, last visited Apr. 21, 2015, 2 Pages.
- Freeman, Jerre Minor, The Punctum Plug: Evaluation of a New Treatment for the Dry Eye, *Transactions American Academy of Ophthalmology and Otolaryngology*, 1975, 874-879, 79.
- Gilbard, Jeffery, Dry Eye, Blepharitis and Chronic Eye Irritation: Divide and Conquer, *J Ophthalmic Nurs. Technol.*, 1999, 109-115,

(56)

References Cited

OTHER PUBLICATIONS

- Goto, Eiki et al, Low-Concentration Homogenized Castor Oil Eye Drops for Noninflamed Obstructive Meibomian Gland Dysfunction, *Ophthalmology*, 2002, 2030-2035, 109.
- Inatomi, Tsutomu et al, Expression of Secretory Mucin Genes by Human Conjunctival Epithelia, *Invest Ophthalmol Vis Sci*, 1996, 1684-1692, 37.
- Kunert, Kathleen et al, Analysis of Topical Cyclosporine Treatment of Patients With Dry Eye Syndrome, *Arch Ophthalmol*, 2000, 1489-1496, 118.
- Lacrisert (hydroxypropyl cellulose ophthalmic insert) Approved Label, downloaded from the FDA website http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/018771s0171bl.pdf, last accessed Apr. 14, 2015, 7 Pages.
- Learn more about Systane Gel Drops at Systane.com, Systane Products, Systane Gel Drops, Downloaded From Alcon Website <http://www.systane.com/Gel-Drops.aspx>, last accessed Apr. 21, 2015.
- Lemp, Michael, Report of the National Eye Institute/Industry Workshop on Clinical Trials in Dry Eyes, CLAO, 1995, 221-232, 21.
- Liu, Kevin et al, Synthetic Approaches to the 2010 New Drugs, *Bioorganic & Medicinal Chemistry*, 2012, 1155-1174, 20.
- Maissa, Cecile et al, Effect of Castor Oil Emulsion Eyedrops on Tear Film Composition and Stability, *Contact Lens & Anterior Eye*, 2010, 76-82, 33.
- Mann, Elaine, Drugs Used in the Treatment of Dry Eye Syndrome, Anti-Inflammatory Drugs and Topical Anti-Allergy Drugs, *Continuing Education & training*, 2007, 30-40.
- Murphy, Rob et al, The Once and Future Treatment of Dry Eye, *Review of Optometry Jan. 2000 Cover Focus*, 2000, 6 Pages (<http://legacy.revoptom.com/archive/Features/ro0200f6.htm>).
- Napper, G. et al, Ocular Therapeutics, *Clin & Exp Optometry*, 2003, 414-415, 86.
- Ophthalmic Drug Products for Over-The-Counter Human Use; Final Monograph, Federal Register, 1988, 7076-7093 (<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Over-theCounterOTCDrugs/StatusofOTCRulemakings/ucm071941.htm>), 53.
- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, patent and exclusivity data for Restasis, downloaded from FDA website http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=050790&Product_No=001&table1=OB_Rx, last accessed Jan. 12, 2015.
- Personal Care Production Council (<http://personalcarecouncil.org/>) 3 Pages, 2015.
- Pflugfelder, Stephen et al, The Diagnosis and Management of Dry Eye: A Twenty-Five-Year Review, *Cornea*, 2000, 644-649, 19(5).
- Restasis Approved Label, download from the Allergan Website (<https://www.restasisprofessional.com/RestasisProfessional/FullPrescribingInformation>) 6 Pages, 2015.
- Rowe, E.L., Effect of Emulsifier Concentration and Type on the Particle Size Distribution of Emulsions, *Journal of Pharmaceutical Science*, 1965, 260-264, 54.
- Solomon, Abraham et al, Doxycycline Inhibition of Interleukin-1 in the Corneal Epithelium, *Ophthalmol Vis Sci*, 2000, 25544-2557, 41.
- Systane Lubricant Eye Drops Information at Systane.com, Systane Products, Systane Balance Lubricant Eye Drops, Download from Alcon Website <http://www.systane.com/systane-Balance-Lubricant-Eye-Drops.aspx>, last accessed Apr. 21, 2015.
- Systane Lubricant Eye Gel, Systane Lubricant Eye Gel, Downloaded from Alcon Website <http://www.systane.com/systane-Lubricant-Eye-Gel.aspx>, last visited Apr. 21, 2015, 2 pages.
- Taban, Mehryar et al, Update on Punctal Plugs, *Comp. Ophthalmology Update*, 2006, 205-212, 7(5).
- Turner, Kathleen et al, Interleukin-6 Levels in the Conjunctival Epithelium of Patients with Dry Eye Disease Treated with Cyclosporine Ophthalmic Emulsion, *Cornea*, Jul. 2000, 492-496, 19(4).
- Yeh, Steven et al, Apoptosis of Ocular Surface Cells in Experimentally Induced Dry Eye, *Invest Ophthalmol Vis*, 2003, 124-129, 44.
- USPTO Before the Patent Trial and Appeal Board, *Apotex Corp., Apotex, Inc. Petitioner v. Allergan, Inc. Patent Owner*, Case IPR2015-01278, Patent 8,633,162, pp. 1-43, Dated Sep. 18, 2015.
- USPTO Before the Patent Trial and Appeal Board, *Apotex Corp., Apotex, Inc. Petitioner v. Allergan, Inc. Patent Owner*, Case IPR2015-01282, Patent 8,629,111, pp. 1-46, Dated Sep. 17, 2015.
- USPTO Before the Patent Trial and Appeal Board, *Apotex Corp., Apotex, Inc. Petitioner v. Allergan, Inc. Patent Owner*, Case IPR2015-01283, Patent 8,685,930, pp. 1-46, Dated Sep. 17, 2015.
- USPTO Before the Patent Trial and Appeal Board, *Apotex Corp., Apotex, Inc. Petitioner v. Allergan, Inc. Patent Owner*, Case IPR2015-01284, Patent 8,648,048, pp. 1-43, Dated Sep. 22, 2015.
- USPTO Before the Patent Trial and Appeal Board, *Apotex Corp., Apotex, Inc. Petitioner v. Allergan, Inc. Patent Owner*, Case IPR2015-01286, Patent 8,642,556, pp. 1-47, Dated Sep. 18, 2015.
- In the United States District Court for the Eastern District of Texas Marshall Division, *Allergan, Inc. (Plaintiff) v. Actavis, Inc., Watson Laboratories, Inc., and Actavis Pharma, Inc. (f/k/a Watson Pharma, Inc.) (defendants)*, C.A. No. 2:14-cv-638-JRG-Lead Case Consolidated with 2:14-cv-188-JRG, Actavis, Inc., Waston Laboratories, Inc., and Actavis Pharma, Inc.'s Invalidity Contentions Pursuant to Local Patent Rules 3-3 and 3-8, pp. 1-74, dated Oct. 15, 2014.
- Letter from Victor Ramsaywak of Apotex, Inc., Notice of Certification Under 21 USC Section 355(j)(2)(B)(ii) (Section 505(j)(2)(B)(ii) of the Federal Food, Drug and Cosmetic Act(and 21 CFR Section 314.95 dated Jul. 23, 2015, pp. 1-116.
- Letter from Shashank Upadhye, Counsel for InnoPharma, Inc., of Amin Talati & Upadhye, Notification of Certification of Invalidity, Unenforceability and/or Non-infringement for U.S. Pat. No. 5,474,979; 8,629,111; 8,633,162; 8,642,556; 8,648,048; and 8,685,930 Pursuant to Section 505(2)(13)(iv) of the Federal Food, Drug, and Cosmetic Act, dated Jul. 31, 2015, pp. 1-98.
- Letter from J.C. Rozendaal of Kellogg, Huber, Hansen, Todd, Evans & Figel, PLLC, Notice of ANDA No. 203880 Concerning Cyclosporine Ophthalmic Emulsion, 0.05% with Paragraph IV Certification Concerning U.S. Pat. Nos. 8,629,111; 8,633,162; 8,642,556; 8,648,048; and 8,685,930 dated Jul. 22, 2015, pp. 1-40.
- Letter from Joseph M. Reisman, Counsel for Mylan Pharmaceuticals Inc., of Knobbe Martens, Cyclosporine Emulsion 0.05%, Route of Administration: Ophthalmic, U.S. Pat. No. 8,629,111; 8,633,162; 8,642,556; 8,648,048; and 8,685,930, Notice of Paragraph IV Certification, dated Jul. 20, 2015, pp. 1-226.
- Letter from Joseph Bonaccorsi, General Counsel, Akorn, Inc., Notification of Certification for U.S. Pat. Nos. 8,629,111; 8,633,162; 8,642,556; 8,648,048; and 8,685,930 Pursuant to Section 505(2)(13)(iv) of the Federal Food, Drug, and Cosmetic Act—21 USC Section 355(j)(2)(B)(iv) Akorn ANDA 204561, dated Jul. 10, 2015, pp. 1-26.
- USPTO Before the Patent Trial and Appeal Board, *Apotex, Inc. Petitioner v. Allergan, Inc. Patent Owner*, Case IPR2015-01278, Patent 8,633,162, pp. 1-63, Dated Jun. 4, 2015.
- USPTO Before the Patent Trial and Appeal Board, *Apotex, Inc. Petitioner v. Allergan, Inc. Patent Owner*, Case IPR2015-01282, Patent 8,629,111, pp. 1-63, Dated Jun. 4, 2015.
- USPTO Before the Patent Trial and Appeal Board, *Apotex, Inc. Petitioner v. Allergan, Inc. Patent Owner*, Case IPR2015-01283, Patent 8,685,930, pp. 1-63, Dated Jun. 4, 2015.
- USPTO Before the Patent Trial and Appeal Board, *Apotex, Inc. Petitioner v. Allergan, Inc. Patent Owner*, Case IPR2015-01284, Patent 8,648,048, pp. 1-63, Dated Jun. 4, 2015.
- USPTO Before the Patent Trial and Appeal Board, *Apotex, Inc. Petitioner v. Allergan, Inc. Patent Owner*, Case IPR2015-01286, Patent 8,642,556, pp. 1-63, Dated Jun. 4, 2015.

* cited by examiner

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