

(12)

(21) 2 467 490

(22) 04.11.2002

(51) Int. Cl.⁷: **A61K 47/38**, A61K 47/02,
A61K 47/10, A61K 47/36,
A61K 31/495

(85) 28.05.2004

(86) PCT/IB02/004612

(87) WO03/045437

(30) 60/334,652 US 30.11.2001

(71) **PFIZER PRODUCTS INC.**,
Eastern Point Road, GROTON, XX (US).

(72) **MOSES, SARA KRISTEN (US).**

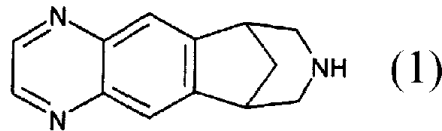
WATERMAN, KENNETH CRAIG (US).
QUAN, ERNEST SHING (US).
SMITH, SCOTT WENDELL (US).
AM ENDE, MARY TANYA (US).
ROY, MICHAEL CHRISTOPHER (US).

(74) **SMART & BIGGAR**

(54) COMPOSITIONS PHARMACEUTIQUES DE 5,7,14-TRIAZATETRACYCLO[10.3.1.0(2,11).0(4,9)]-HEXADECA-2(11)3,5,7,9-PENTAENE

(54) PHARMACEUTICAL COMPOSITIONS OF 5,7,14-TRIAZATETRACYCLO[10.3.1.0(2,11).0(4,9)]-HEXADECA-2(11)3,5,7,9-PENTAENE

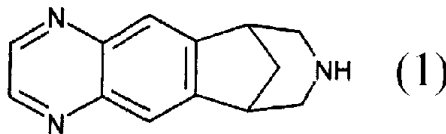
(57) The present invention is directed to controlled-release (CR) oral pharmaceutical dosage forms of 5,8,14-triazatetracyclo[10.3.1.0(2,11).0(4,9)]-hexadeca-2(11), 3,5,7,9-pentaene, 1, and pharmaceutically acceptable salts thereof, and methods of using them to reduce nicotine addiction or aiding in the cessation or lessening of tobacco use while reducing nausea as an adverse effect. The present invention also relates to an immediate-release (IR) low dosage composition having a stable formulation with uniform drug distribution and potency.



(86) Date de dépôt PCT/PCT Filing Date: 2002/11/04
(87) Date publication PCT/PCT Publication Date: 2003/06/05
(85) Entrée phase nationale/National Entry: 2004/05/28
(86) N° demande PCT/PCT Application No.: IB 2002/004612
(87) N° publication PCT/PCT Publication No.: 2003/045437
(30) Priorité/Priority: 2001/11/30 (60/334,652) US

(51) Cl.Int.⁷/Int.Cl.⁷ A61K 47/38, A61K 31/495, A61K 47/36,
A61K 47/10, A61K 47/02
(71) Demandeur/Applicant:
PFIZER PRODUCTS INC., US
(72) Inventeurs/Inventors:
AM ENDE, MARY TANYA, US;
ROY, MICHAEL CHRISTOPHER, US;
SMITH, SCOTT WENDELL, US;
WATERMAN, KENNETH CRAIG, US;
MOSES, SARA KRISTEN, US;
QUAN, ERNEST SHING, US
(74) Agent: SMART & BIGGAR

(54) Titre : COMPOSITIONS PHARMACEUTIQUES DE 5,7,14-TRIAZATETRACYCLO[10.3.1.0^{2,11}.0(4,9)]-HEXADECA-
2(11)3,5,7,9-PENTAENE
(54) Title: PHARMACEUTICAL COMPOSITIONS OF 5,7,14-TRIAZATETRACYCLO[10.3.1.0(2,11).0(4,9)]-HEXADECA-
2(11)3,5,7,9-PENTAENE



(57) Abrégé/Abstract:

The present invention is directed to controlled-release (CR) oral pharmaceutical dosage forms of 5,8,14-triazatetracyclo[10.3.1.0^{2,11}.0^{4,9}]-hexadeca-2(11),3,5,7,9-pentaene, 1, and pharmaceutically acceptable salts thereof, and methods of using them to reduce nicotine addiction or aiding in the cessation or lessening of tobacco use while reducing nausea as an adverse effect. The present invention also relates to an immediate-release (IR) low dosage composition having a stable formulation with uniform drug distribution and potency.

Canada

<http://opic.gc.ca> • Ottawa-Hull K1A 0C9 • <http://cipo.gc.ca>

OPIC • CIPO 191

OPIC



CIPO

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
5 June 2003 (05.06.2003)

PCT

(10) International Publication Number
WO 03/045437 A1

(51) International Patent Classification⁷: **A61K 47/38**,
47/36, 47/02, 47/10, 31/495

Sara, Kristen [US/US]; Pfizer Global Research and Development, Eastern Point Road, Groton, CT 06340 (US).
QUAN, Ernest, Shing [US/US]; Pfizer Global Research and Development, Eastern Point Road, Groton, CT 06340 (US).

(21) International Application Number: PCT/IB02/04612

(22) International Filing Date:
4 November 2002 (04.11.2002)

(74) Agents: **LUMB, J., Trevor** et al.; Pfizer Inc., 201 Tabor Road, Morris Plains, NJ 07950 (US).

(25) Filing Language: English

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(26) Publication Language: English

(30) Priority Data:
60/334,652 30 November 2001 (30.11.2001) US

(71) Applicant (*for all designated States except US*): **PFIZER PRODUCTS INC.** [US/US]; Eastern Point Road, Groton, CT 06340 (US).

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(72) Inventors; and

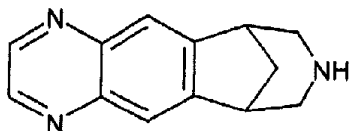
(75) Inventors/Applicants (*for US only*): **AM ENDE, Mary, Tanya** [US/US]; Pfizer Global Research and Development, Eastern Point Road, Groton, CT 06340 (US). **ROY, Michael, Christopher** [US/US]; Pfizer Global Research and Development, Eastern Point Road, Groton, CT 06340 (US). **SMITH, Scott, Wendell** [US/US]; Pfizer Global Research and Development, 10777 Science Center Drive, San Diego, CA 92121 (US). **WATERMAN, Kenneth, Craig** [US/US]; Pfizer Global Research and Development, Eastern Point Road, Groton, CT 06340 (US). **MOSES,**

Published:

— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PHARMACEUTICAL COMPOSITIONS OF 5,7,14-TRIAZATETRACYCLO[10.3.1.0(2,11).0(4,9)]-HEXADECA-2(11)3,5,7,9-PENTAENE



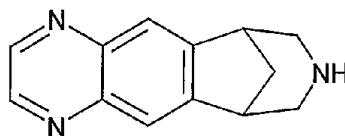
(1)

(57) Abstract: The present invention is directed to controlled-release (CR) oral pharmaceutical dosage forms of 5,8,14-triazatetracyclo[10.3.1.0^{2,11}.0^{4,9}]-hexadeca-2(11),3,5,7,9-pentaene, 1, and pharmaceutically acceptable salts thereof, and methods of using them to reduce nicotine addiction or aiding in the cessation or lessening of tobacco use while reducing nausea as an adverse effect. The present invention also relates

to an immediate-release (IR) low dosage composition having a stable formulation with uniform drug distribution and potency.

WO 03/045437 A1

The present invention is directed to controlled-release (CR) oral pharmaceutical dosage forms of 5,8,14-triazatetracyclo[10.3.1.0^{2,11}.0^{4,9}]-hexadeca-2(11),3,5,7,9-pentaene, **1**, and related compounds, and methods of using them to reduce nicotine addiction or aiding in the cessation or lessening of tobacco use while reducing nausea as an adverse effect. The present invention also relates to an immediate-release (IR) low dosage composition having a stable formulation with uniform drug distribution and potency.



1

BACKGROUND OF THE INVENTION

Compound **1**, also known as 7,8,9,10-tetrahydro-6,10-methano-6H-pyrazino[2,3-h][3]-benzazepine, binds to neuronal nicotinic acetylcholine specific receptor sites and are useful in modulating cholinergic function. Accordingly, this compound is useful in the treatment of inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amyotrophic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac arrhythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supranuclear palsy, chemical dependencies and addictions (e.g., dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, barbiturates, opioids or cocaine), headache, migraine, stroke, traumatic brain injury (TBI), obsessive-compulsive disorder (OCD), psychosis, Huntington's chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age-related cognitive decline, epilepsy, including petit mal absence epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome.

Compound **1** and pharmaceutically acceptable acid addition salts thereof are referred to in International Patent Publication WO 99/35131, published July 15, 1999, which is incorporated herein by reference in its entirety.

Whereas immediate release (IR) dosage forms of the aforementioned compound, that is, dosage forms designed to provide the drug in a dissolved form upon swallowing in less than about 30 minutes, provide therapeutically useful levels of drug in the blood and brain, it has been observed that there is a significant level of nausea in patients, especially at doses sufficiently high to be therapeutically useful for some patients. Since nausea can lead

to poor patient compliance with a dosing regimen, there is a need to provide 1 in a form that reduces the incidence of nausea.

Accordingly, the present invention provides CR dosage forms of 1 that reduce or eliminate nausea while maintaining a therapeutic level of the drug in the blood and central nervous system (CNS). While examples exist in the art suggesting that CR dosage forms may in some cases provide for a reduction in such side effects as nausea (e.g., oxycodone (J. R. Caldwell, *et al.*, *J. of Rheumatology*, 1999, 26, 862-869), venlafaxine (R. Entsuah and R. Chitra, *Psychopharmacology Bulletin*, 1997, 33, 671-676) and paroxetine (R. N. Golden, *et al.*, *J. Clin. Psychiatry*, 2002, 63, 577-584), counter examples also exist which indicate that CR dosage forms are sometimes no better than immediate release dosage forms for the reduction of nausea, and therefore teach away from the utility of the CR form as a means of reducing side effects. Examples of this teaching away include morphine sulfate (T. D. Walsh, *et al.*, *J. Clin. Oncology*, 1992, 15, 268-272), hydromorphone (H. Hays, *et al.*, *Cancer*, 1994, 74, 1808-1816), dihydrocodeine tartrate (G. Xu, *et al.*, *Zhongguo Yaowu Yilaixing Zazhi*, 1999, 8, 52-57) and carbidopa/levodopa (G. Block, *et al.*, *European Neurology*, 1997, 37, 23-27). In addition, in many cases, CR dosage forms result in reduction in bioavailability compared to the IR dosage form, necessitating an increase in dose or even making the use of a CR dosage form infeasible. It therefore remains impossible to predict *a priori* which drugs showing nausea will actually benefit from CR dosage forms. Moreover, the rate at which the drug is made available, that is, its dissolution rate, can range considerably from slightly slower than the IR dosage form to deliver over an extended period (up to about 24 hours). The inventors have discovered that for 1, CR dosage forms with a certain range of delivery rates will provide therapeutic blood and CNS drug levels while reducing the incidence of nausea when compared to the IR dosage form. The inventors have also discovered specific preferred ways of formulating 1 to achieve the desired drug administration rates. The inventors have also discovered preferred dosing regimens that provide therapeutic drug levels while maintaining low levels of nausea.

The high potency of compound 1 as a nicotinic receptor ligand allows the use of low dosage strengths for administration. For ease of handling, manufacturing and patient convenience, low dosage strength drugs are often formulated at high dilution with excipients. In the preparation and storage of such dilute formulations, however, unique challenges are introduced. First, the high dilution can enable excipients or even excipient impurities to cause significant drug degradation during storage. Examples of excipient properties that may impact drug degradation include moisture content and mobility of moisture (see J.T. Carstensen, *Drug Stability: Principles and Practices*, 2nd Ed, Marcel Dekker, NY, 1995, 449-452), and excipient acidity affecting local pH microenvironments (see K. Waterman *et al.*, *Pharm Dev. Tech.*, 2002, 7(2), 113-146). Examples of excipient impurities that affect drug

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.