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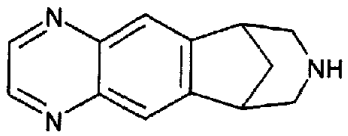
(54) COMPOSITIONS PHARMACEUTIQUES DE 5,7,14-TRIAZATETRACYCLO[10.3.1.0(2,11).0(4,9)]-HEXADECA-2(11)3,5,7,9-PENTAENE

(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[10.3.1.02,11.04,9]- 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.



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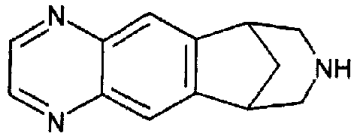

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(57) Abrégé/Abstract:
The present invention is directed to controlled-release (CR) oral pharmaceutical dosage forms of 5,8,14-triazatetracyclo[10.3.1.$0^{2.11}$.$0^{4.9}$]-hexadeca-2(11),3,5,7,9-pentaene, 1, and pharmaceutically acceptable salts thereof, 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.

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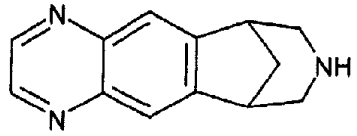

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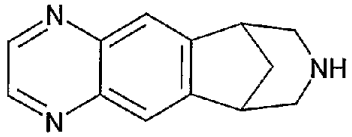
(57) Abstract: The present invention is directed to controlled-release (CR) oral pharmaceutical dosage forms of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene, 1, and pharmaceutically acceptable salts thereof, and methods of using them to reduce nicotine addiction 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.

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

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.



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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

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