

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
13 November 2008 (13.11.2008)

PCT

(10) International Publication Number  
WO 2008/137960 A1

(51) International Patent Classification:  
A61K 31/55 (2006.01)

(74) Agents: GRUMBLING, Matthew, V. et al.; Wilson Son-  
sini Goodrich & Rosati, 650 Page Mill Road, Palo Alto, CA  
94304-1050 (US).

(21) International Application Number:  
PCT/US2008/062961

(81) Designated States (*unless otherwise indicated, for every  
kind of national protection available*): AE, AG, AL, AM,  
AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA,  
CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE,  
EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID,  
IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC,  
LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN,  
MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH,  
PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV,  
SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN,  
ZA, ZM, ZW.

(22) International Filing Date: 7 May 2008 (07.05.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/916,550 7 May 2007 (07.05.2007) US

(84) Designated States (*unless otherwise indicated, for every  
kind of regional protection available*): ARIPO (BW, GH,  
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,  
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),  
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,  
FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL,  
NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG,  
CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (*for all designated States except US*):  
QUESTOR PHARMACEUTICALS, INC. [US/US];  
3260 Whipple Road, Union City, CA 94587 (US).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): CARTT, Steve  
[US/US]; 3260 Whipple Road, Union City, CA 94587  
(US). MEDEIROS, David [US/US]; 212 Crown Circle,  
So. San Francisco, CA 94080 (US).

Published:

— with international search report



WO 2008/137960 A1

(54) Title: NASAL ADMINISTRATION OF BENZODIAZEPINES

(57) Abstract: Particulate formulations of benzodiazepines, such as diazepam, are used for nasal administration of diazepam drugs to patients. Multimodal particulate formulations of benzodiazepines and methods for their use, e.g. by nasal administration for the treatment of seizure, are also provided.

## NASAL ADMINISTRATION OF BENZODIAZEPINES

[0001] This application claims benefit of priority of provisional application United States serial number 60/916,550, filed on May 7, 2007, the entire contents of which are incorporated herein by reference.

### FIELD OF THE INVENTION

5 [0002] This application relates to the administration of benzodiazepine drugs, and in particular to the nasal administration of benzodiazepine drugs.

### BACKGROUND OF THE INVENTION

10 [0003] Benzodiazepines, such as diazepam, lorazepam and medazepam, make up a class of psychoactive drugs. Most benzodiazepines are classified as anxiolytic, sedative and/or hypnotic. The class of benzodiazepines are minor tranquilizers possessing varying hypnotic, sedative, anxiolytic, anticonvulsant, muscle relaxant and amnesic properties. Various benzodiazepines are useful in treating anxiety, insomnia, agitation, seizures, and muscle spasms, as well as alcohol withdrawal. They can also be used before certain medical procedures such as endoscopies, dental work, or other medical procedures where tension and anxiety are present, and prior to some medical procedures in order to induce amnesia.

15 [0004] As anti-convulsants, benzodiazepines may be used separately or in adjunctive therapy. Various formulations for treatment of seizure with benzodiazepines have been developed. Generally speaking, the oral route of administration is considered sub-optimal for acute treatment of seizures, as the amount of time require for the drug to reach therapeutically relevant concentrations in the blood plasma is rather long – as much as an hour. Moreover, some benzodiazepines, such as diazepam, have poor oral bioavailability and/or suffer from significant first-pass liver effects. Alternatives to oral dosing of benzodiazepines, including diazepam, have been developed.

20 [0005] These alternatives include intravenous, suppository and intranasal formulations. The intravenous route provides perhaps the fastest route of administration to date; however intravenous administration is generally limited to trained health care professionals (e.g. nurses). Thus, the intravenous administration of benzodiazepines for acute treatment of seizure is limited to tightly controlled clinical settings, such as emergency rooms and in-patient hospital and/or hospice care.

25 [0006] Suppository formulations of benzodiazepines have a rapid onset of action and require little professional expertise for their administration. However, the inconvenience of suppositories is an obvious impediment to their being administered by anyone outside a very small group of the patient's intimate acquaintances and the patient's professional medical caretakers. Thus, while suppository formulations have found some success in the treatment of children by their parents or guardians, they are unlikely to gain widespread acceptance as a means for acute treatment of seizure in adults outside controlled clinical environments.

30 [0007] Nasal formulations of benzodiazepines have been suggested for the acute treatment of seizure. Benzodiazepines are quickly absorbed and transported across the mucosa of the nasal sinuses, which results in fast achievement of pharmaceutically effective plasma levels. However, the utility of the existing nasal benzodiazepine formulations has been limited to a degree by the poor solubility of such benzodiazepines as diazepam. Nasal preparations are generally administered in metered sprays having volumes of less than 250  $\mu$ l,

preferably less than 150  $\mu$ l, and ideally from 25 to 100  $\mu$ l, since administration of larger volumes usually exceeds the capacity of the nasal sinuses and results in volumes in excess of about 250  $\mu$ l bypassing the sinuses and flowing down the back of the throat where it is swallowed. As smaller dose volumes are preferred for nasal administration, poor water solubility of benzodiazepines limits the effective dose that may be administered to a patient at any given time. This in turn limits the clinical effectiveness of nasally-administered benzodiazepines for the acute treatment of seizure.

[0008] There is a need for benzodiazepine formulations that are capable of providing to the nasal mucosa sufficient quantity of benzodiazepine in a small enough volume to provide therapeutically effective blood plasma concentration of benzodiazepine within a short period after administration of the formulation to the nasal mucosa. There is also a need for methods of treating a variety of disorders, including anxiety and seizure, by administering a therapeutically effective amount of a benzodiazepine drug to the nasal mucosa. In particular, there is a need for an intranasal formulation of diazepam that is capable of producing anticonvulsant effective blood plasma levels within a short period after having been administered to a patient. There is also a need for a method of providing acute relief from seizure to a patient within a short period after administering a benzodiazepine, such as diazepam, to the patient. These and other objects and advantages are provided by the invention described herein.

#### SUMMARY OF THE INVENTION

[0009] The foregoing and further needs are met by embodiments of the present invention, which provide a composition for nasal administration of a medicament, comprising a first population of particles having a first effective mean particle diameter and a second population of particles having a second effective mean particle diameter, wherein the first effective mean particle diameter is at least 1.5 times, at least 1.6 times, at least 1.7 times, at least 1.8 times, at least 1.9 times, at least 2 times, at least 2.5 times or at least 3 times that of the second effective mean particle diameter.

[0010] The foregoing and further needs are met by embodiments of the present invention, which provide a composition for nasal administration of a medicament, comprising a first population of particles having a first effective mean particle diameter and a second population of particles having a second effective mean particle diameter, wherein the first effective mean particle diameter is at least twice that of the second effective mean particle diameter.

[0011] The foregoing and further needs are met by embodiments of the present invention, which provide a method of using a composition for nasal administration of a medicament, comprising a first population of particles having a first effective mean particle diameter and a second population of particles having a second effective mean particle diameter, wherein the first effective mean particle diameter is at least 1.5 times, at least 1.6 times, at least 1.7 times, at least 1.8 times, at least 1.9 times, at least 2 times, at least 2.5 times or at least 3 times that of the second effective mean particle diameter. The method comprises administering an effective amount of the composition to the nose by administering a therapeutically effective amount of the composition to at least one nostril.

[0012] The foregoing and further needs are met by embodiments of the present invention, which provide a method of using a composition for nasal administration of a medicament, comprising a first population of particles having a first effective mean particle diameter and a second population of particles having a second

effective mean particle diameter, wherein the first effective mean particle diameter is at least twice that of the second effective mean particle diameter. The method comprises administering an effective amount of the composition to the nose by administering a therapeutically effective amount of the composition to at least one nostril.

5 [0013] The foregoing and further needs are met by embodiments of the present invention, which provide a pharmaceutical particulate composition for nasal delivery of a medicament comprising particulates having a multimodal particle size distribution.

[0014] The foregoing and further needs are met by embodiments of the present invention, which provide a method of using a pharmaceutical particulate composition for nasal delivery of a medicament comprising  
10 particulates having a multimodal particle size distribution, comprising administering an effective amount of the composition to the nose by administering a therapeutically effective amount of the composition to at least one nostril.

[0015] The foregoing and further needs are further met by embodiments of the present invention, which provide an aerosol composition of an aqueous suspension or dispersion of nanoparticulate benzodiazepine  
15 particles, wherein: the droplets of the aerosol have a mass median aerodynamic diameter (MMAD) less than or equal to about 1000  $\mu\text{m}$  and the nanoparticulate benzodiazepine particles have an effective average particle size of less than about 5000 nm.

[0016] The foregoing and further needs are further met by embodiments of the present invention, which provide a method of using an aerosol composition of an aqueous suspension or dispersion of nanoparticulate  
20 benzodiazepine particles, wherein: the droplets of the aerosol have a mass median aerodynamic diameter (MMAD) less than or equal to about 1000  $\mu\text{m}$  and the nanoparticulate benzodiazepine particles have an effective average particle size of less than about 5000 nm, the method comprising administering an effective amount of the composition to the nose by spraying a therapeutically effective amount of the composition into at least one nostril.

25 [0017] The foregoing and further needs are met by embodiments of the present invention, which provide a method of administering a benzodiazepine drug to a patient, comprising administering to the nose or nasal cavity an effective amount of an aerosol composition of an aqueous suspension or dispersion of nanoparticulate benzodiazepine particles, wherein: the droplets of the aerosol have a mass median aerodynamic diameter (MMAD) less than or equal to about 1000  $\mu\text{m}$  and the nanoparticulate benzodiazepine particles have an effective  
30 average particle size of less than about 5000 nm.

[0018] The foregoing and further needs are additionally met by embodiments of the present invention, which provide a pharmaceutical composition for nasal administration of benzodiazepine comprising benzodiazepine particles and one or more non-cationic surface active agents adsorbed to a surface thereof.

[0019] The foregoing and further needs are further met by embodiments of the invention, which provides a  
35 method of administering a pharmaceutical composition for nasal administration of benzodiazepine comprising benzodiazepine particles and one or more non-cationic surface active agents adsorbed to a surface thereof, the method comprising administering an effective amount of the composition to the nose by administering a therapeutically effective amount of the composition to at least one nostril.

[0020] The foregoing and further needs are met by embodiments of the present invention, which provide a  
40 method of administering a benzodiazepine drug to a patient, comprising administering to the patient's nose or

nasal cavity a pharmaceutical composition comprising particles of a benzodiazepine drug having a surface active agent adsorbed to a surface thereof.

[0021] The foregoing and further needs are met by embodiments of the present invention, which provide a non-aqueous dispersion or suspension of nanoparticulate benzodiazepine particles.

5 [0022] The foregoing and additional needs are further met by embodiments of the present invention, which provide a method of administering a non-aqueous dispersion or suspension of nanoparticulate benzodiazepine particles, the method comprising administering an effective amount of the dispersion or suspension to the nose by administering a therapeutically effective amount of the composition to at least one nostril.

10 [0023] The foregoing and further needs are additionally met by embodiments of the present invention, which provide, a method of administering a benzodiazepine drug to a patient, comprising administering to the patient's nose or nasal cavity a pharmaceutical composition comprising a non-aqueous dispersion or suspension of nanoparticulate benzodiazepine particles.

15 [0024] The foregoing and additional needs are further met by embodiments of the invention, which provide a nanoparticulate composition comprising: (a) a benzodiazepine having an effective average particle size of less than about 2000 nm, wherein the benzodiazepine is selected from the group consisting of alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, diazepam, nitrazepam, oxazepam, midazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, lopraxolam, pharmaceutically acceptable salts and esters thereof, and mixtures thereof; and (b) at least one surface stabilizer. In some embodiments, the surface stabilizer is  
20 selected from the group consisting of a nonionic surfactant, an ionic surfactant, a cationic surfactant, an anionic surfactant, and a zwitterionic surfactant.

[0025] The foregoing and additional needs are further met by a method of treating a subject in need comprising administering to the subject a nanoparticulate benzodiazepine composition comprising: (a) a benzodiazepine having an effective average particle size of less than about 2000 nm, wherein the benzodiazepine is selected  
25 from the group consisting of alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, diazepam, nitrazepam, oxazepam, midazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, lopraxolam, pharmaceutically acceptable salts and esters thereof, and mixtures thereof; and (b) at least one surface stabilizer. In some embodiments, the surface stabilizer is selected from the group consisting of a nonionic surfactant, an  
30 ionic surfactant, a cationic surfactant, an anionic surfactant, and a zwitterionic surfactant.

[0026] These and further advantages and characteristics of the present invention will become apparent to the person skilled in the art upon consideration of the description and claims.

#### INCORPORATION BY REFERENCE

35 [0027] All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

# 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.