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Entry into the European phase (EPO as designated or elected Office)

To the European Patent Office

European application number	EP12801372.9
PCT application number	PCT/US2012/042311
PCT publication number	WO2012174158
Applicant's or representative's reference	EPA-124 519
International Filing Date	13.06.2012
International Searching Authority (ISA)	US
International Preliminary Examining Authority (IPEA)	not applicable

1. Applicant

Indications concerning the applicant(s) are contained in the international publication or were recorded by the International Bureau after the international publication. ☒

Changes which have not yet been recorded by the International Bureau are set out here: ☐

2. Representative

This is the representative who will be listed in the Register of European Patents and to whom notifications will be made

Representative 1

Name: WICHMANN Hendrik

Company: Wuesthoff & Wuesthoff Patent- und Rechtsanwaelte

Address of place of business: Schweigerstr. 2

81541 Muenchen,

Germany

Telephone: 089-62 18 00-0

Fax: 089 / 621800-15

e-mail: wuesthoff@wuesthoff.de

3. Authorisation

An individual authorisation is attached. ☐

A general authorisation has been registered under No: ☐

A general authorisation has been filed, but not yet registered. ☐

The authorisation filed with the EPO as PCT receiving Office expressly includes the European phase. ☐

4. Request for examination

Examination of the application under Art. 94 EPC is hereby requested. The examination fee is being (has been, will be) paid. ☒

Request for examination in an admissible non-EPO language: ☐

The applicant waives his right to be asked under Rule 70(2) EPC whether he wishes to proceed further with the application. ☐

5. Copies

Additional copies of the documents cited in the supplementary European search report are requested. ☐

Number of additional sets of copies

6. Documents intended for proceedings before the EPO

Number of claims on entry into the European phase: 65

6.1 Proceedings before the EPO as designated Office (PCT I) are to be based on the following documents:

the application documents published by the International Bureau (with all claims, description and drawings), where applicable with amended claims under Art. 19 PCT ☒

unless replaced by the amendments attached. ☐

Where necessary, clarifications should be attached as `Other documents`

6.2 Proceedings before the EPO as elected Office (PCT II) are to be based on the following documents:

the documents on which the international preliminary examination report is based, including any annexes ☐

unless replaced by the amendments attached. ☐

Where necessary, clarifications should be attached as `Other documents`

If the EPO as International Preliminary Examining Authority has been supplied with test reports, these may be used as the basis of proceedings before the EPO. ☐

6.3 A copy of the results of the search carried out by the authority with which the previous application(s) whose priority is claimed was (were) filed is attached (R. 141(1) EPC). ☐

6.4 The applicant waives his right to the communication under Rules 161(1) or (2) and 162 EPC. ☐

7. Translations

Translations in one of the official languages of the EPO (English, French, German) are attached as crossed below: ☐

** In proceedings before the EPO as designated or elected Office (PCT I + II):*

Translation of the international application (description, claims, any text in the drawings) as originally filed, of the abstract as published and of any indication under Rule 13bis.3 and 13bis.4 PCT regarding biological material ☐

Translation of the priority application(s) (to be filed only at the EPO's request, Rule 53(3) EPC) ☐

It is hereby declared that the international application as originally filed is a complete translation of the previous application (Rule 53(3) EPC) ☐

** In addition, in proceedings before the EPO as designated Office (PCT I):*

Translation of amended claims and any statement under Art. 19 PCT, if the claims as amended are to form the basis for the proceedings before the EPO (see Section 6). ☐

** In addition, in proceedings before the EPO as elected Office (PCT II):*

Translation of annexes to the international preliminary examination report ☐

8. Biological material

The invention uses and/or relates to biological material deposited under Rule 31 EPC. ☐

The particulars referred to in Rule 31(1)(c) EPC (if not yet known, the depositary institution and the identification reference(s)) [number, symbols, etc.] of the depositor) are given in the international publication or in the translation submitted in Section 7 on: ☐

page(s) / line(s)

The receipt(s) of deposit issued by the depositary institution

is (are) enclosed. ☐

will be filed later. ☐

Waiver of the right to an undertaking from the requester pursuant to Rule 33(2) EPC attached. ☐

9. Nucleotide and amino acid sequences

The international application discloses nucleotide and/or amino acid sequences. ☐

9.1 The sequence listing was filed under Rule 5.2(a) PCT, or furnished to the EPO as ISA under Rule 13ter.1(a) PCT, or is otherwise available to the EPO, in computer-readable format in accordance with WIPO ST.25. ☐

9.2

The sequence listing is attached in computer-readable format in accordance with WIPO Standard ST.25 ☐

The sequence listing is attached in PDF format. ☐

The sequence listing does not include matter which goes beyond the content of the application as filed. ☐

10. Designation fees

All the contracting states party to the EPC at the time of filing of the international patent application and designated in the international application are deemed to be designated (see Article 79(1) EPC). ☒

The following states, which were contracting states to the EPC at the time of filing of the international application, are designated:

AL AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR

11. Extension of the European patent

This application is deemed to be a request to extend the European patent application and the European patent granted in respect of it to all the non-contracting states to the EPC designated in the international application and with which extension agreements are in force on the date on which the international application is filed. However, the extension only takes effect if the prescribed extension fee is paid. ☐

It is currently intended to pay the extension fee for the following states:

Note: Under the automatic debiting procedure, extension fees will only be debited for states indicated here, unless the EPO is instructed otherwise before expiry of the period for payment.

12. List of enclosed documents

	Description of document	Original file name	Assigned file name

13. Mode of payment: Debit from deposit account ☒

Currency: EUR

The European Patent Office is hereby authorised, to debit from the deposit account with the EPO any fees and costs indicated on the fees page.

Deposit account number: 28000226

Account holder: Wuesthoff & Wuesthoff

14. Any refunds should be made to the following EPO deposit account: ☒

Number and account holder: Wuesthoff & Wuesthoff, 28000226

15. Fees

		Factor/reduction applied	Fee schedule	Amount to be paid
15-1	002 Fee for a European search - Applications filed on/after 01.07.2005	-190	1 165.00	975.00
15-2	005e Designation fee - For all contracting States designated for applications filed on/after 01.04.2009	1	555.00	555.00
15-3	006 Examination fee - For applications filed on/after 01.07.2005	1	1 555.00	1 555.00
15-4	015 Claims fee - For the 16th to the 50th claim	0	225.00	0.00
15-5	15e Claims fee - For the 51st and each subsequent claim	0	555.00	0.00
15-6	020 Filing fee - entry EP phase - online	1	115.00	115.00
15-7	520 Additional filing fee for the 36th and each subsequent page - entry into EP phase	42	14.00	588.00
	Total:		EUR	**3 788.00**

16. Annotations

17. Signature(s) of applicant(s) or representative

Place: **München**

Date: **07 January 2014**

Signed by: **/Dr. Hendrik Wichmann, European Patent Attorney/**

Capacity: **(Representative)**

Table for section 6 of Form 1200.3

In accordance with the Notice from the European Patent Office dated 26 January 2009 concerning the 2009 fee structure (OJ EPO 2009, 118, and Guidelines for Examination in the EPO, April 2009, A-III, 13.2), the amount of the additional fee (Art. 2, item 1a, Rules relating to Fees) for the pages of this European patent application is calculated as follows:

Documents intended for proceedings before the EPO (R. 159 (1) (b) EPC) and for calculating the additional fee (Art. 2, item 1a, RFees):

		Page(s) from ... to ...	Number of pages
Description:	International application as published	1-65	65
Claims:	International application as published	66-71	6
Drawings:	International application as published	1/5-5/5	5
Abstract:	Default count: one page		1
Total number of pages			77
Fee-exempt pages (Art. 2, item 1a, RFees)			-35
Number of pages to be paid for			42
			(x 14 EUR per page)
Total amount payable		EUR	588

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Acknowledgement of receipt

We hereby acknowledge receipt of the form for entry into the European phase (EPO as designated or elected Office) as follows:

Submission number	2510119
PCT application number	PCT/US2012/042311
EP application number	12801372.9
Date of receipt	07 January 2014
Receiving Office	European Patent Office, The Hague
Your reference	EPA-124 519
Applicant	
Country	
Documents submitted	package-data.xml application-body.xml ep-euro-pct.xml epf1200.pdf (4 p.)
Submitted by	CN=Beate Meiners 24076
Method of submission	Online
Date and time receipt generated	07 January 2014, 13:34 (CET)
Message Digest	9B:D4:E4:9A:F1:A1:EA:F8:BA:B4:4F:E7:22:C3:65:41:AF:B2:DD:19

Correction by the EPO of errors in debit instructions filed by eOLF
Errors in debit instructions filed by eOLF that are caused by the editing of Form 1038E entries or the continued use of outdated software (all forms) may be corrected automatically by the EPO, leaving the payment date unchanged (see decision T 152/82, OJ EPO 1984, 301 and point 6.3 ff ADA, Supplement to OJ EPO 10/2007).

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Date
24.01.14

Reference	Application No./Patent No.
	12801372.9 - 1453 PCT/US2012042311

Applicant/Proprietor
Hale BioPharma Ventures, LLC

Notification of the data mentioned in Rule 19(3) EPC

In the above-identified patent application you are designated as inventor/co-inventor.
Pursuant to Rule 19(3) EPC the following data are notified herewith:

DATE OF FILING	: 13.06.12
PRIORITY	: US/14.06.11/ USP201161497017 : US/13.12.11/ USP201161570110
TITLE	: ADMINISTRATION OF BENZODIAZEPINE
DESIGNATED STATES	: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR

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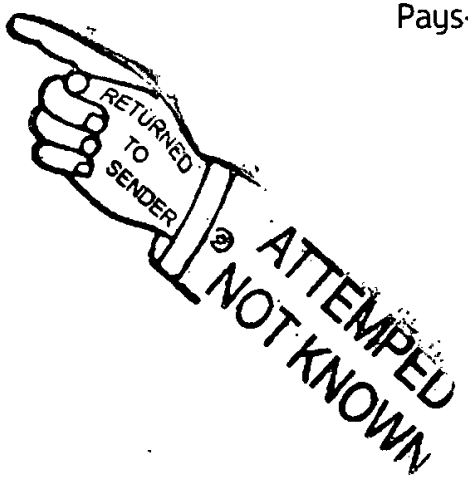

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TITLE	: ADMINISTRATION OF BENZODIAZEPINE
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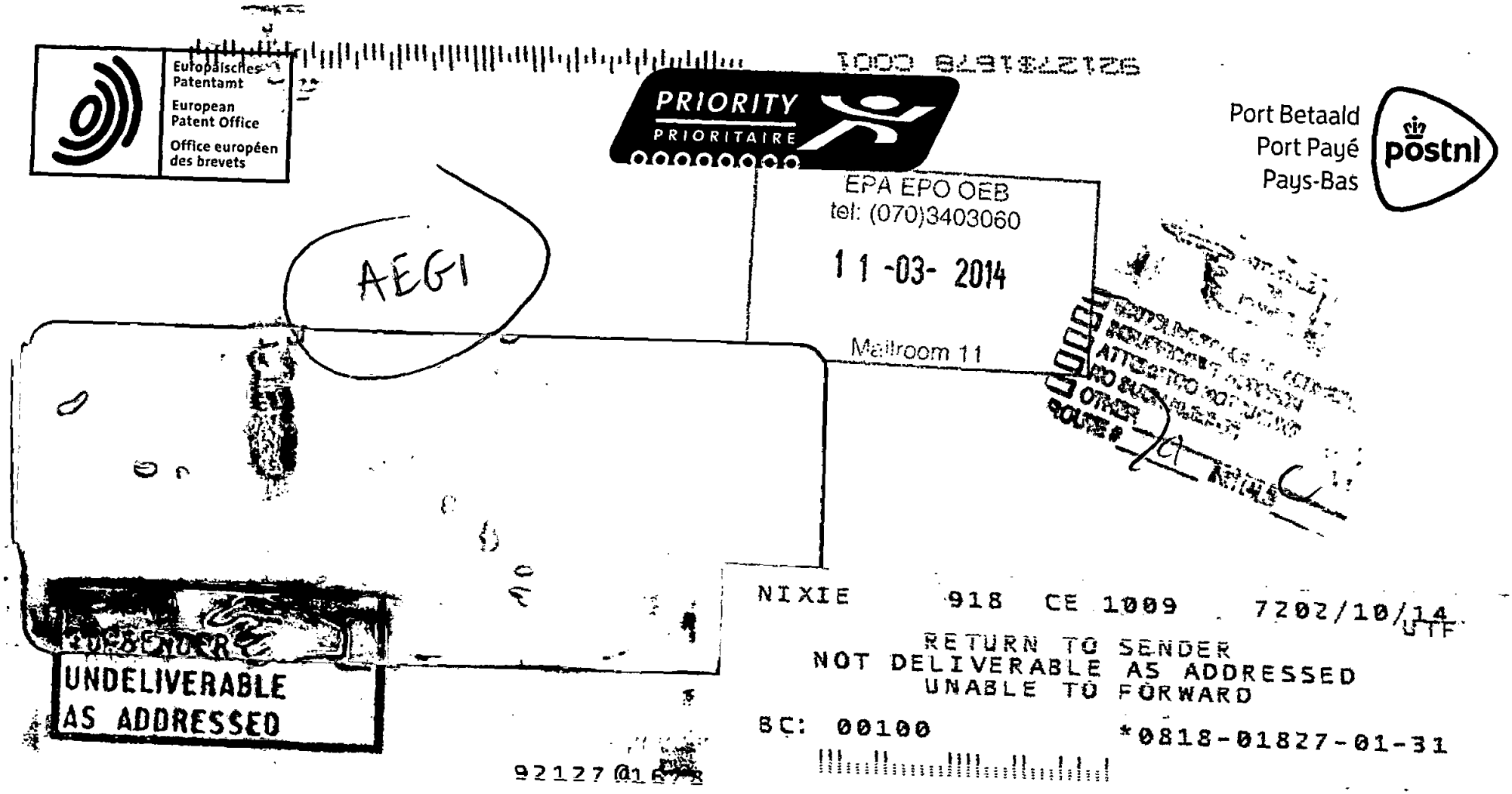
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Questions about this communication ?
Contact Customer Services at www.epo.org/contact

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Date
26.03.14

Reference	Application No./Patent No.
EPA-124 519	12801372.9 - 1453 / 2720699 PCT/US2012042311
Applicant/Proprietor	
Hale BioPharma Ventures, LLC	

Communication of European publication number and information on the application of Article 67(3) EPC

The provisional protection under Article 67(1) and (2) EPC in the individual Contracting States becomes effective only when the conditions referred to in Article 67(3) EPC have been fulfilled (for further details, see information brochure of the European Patent Office "National Law relating to the EPC" and additional information in the Official Journal of the European Patent Office).

Pursuant to Article 153(3) EPC the publication under Article 21 PCT of an international application for which the European Patent Office is a designated or elected Office takes the place of the publication of a European patent application.

The bibliographic data of the above-mentioned Euro-PCT application will be published on 23.04.14 in Section I.1 of the European Patent Bulletin. The European publication number is 2720699.

In all future communications to the European Patent Office, please quote the application number plus Directorate number.

Receiving Section

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 35401-716602	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2012/042311	International filing date *(day/month/year)* 13 June 2012 (13.06.2012)	Priority date *(day/month/year)* 14 June 2011 (14.06.2011)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant HALE BIOPHARMA VENTURES, LLC		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 25 March 2014 (25.03.2014)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Lingfei Bai e-mail: pt02.pct@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: MATTHEW V. GRUMBLING
WILSON SONSINI GOODRICH & ROSATI
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PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	31 AUG 2012

Applicant's or agent's file reference	FOR FURTHER ACTION
35401-716.602	See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 12/42311	13 June 2012 (13.06.2012)	14 June 2011 (14.06.2011)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A01N 43/62; A61K 31/55 (2012.01)
USPC - 514/220-221

Applicant HALE BIOPHARMA VENTURES, LLC

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1 *bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Fom PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	10 August 2012 (10.08.2012)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (July 2011)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

      ☐ on paper

      ☐ in electronic form

   b. (time)

      ☐ in the international application as filed

      ☐ together with the international application in electronic form

      ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 63-65

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 63-65 are so unclear that no meaningful opinion could be formed *(specify)*:

Claims 63-65 are improper multiple dependent claims because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for said claims Nos. 63-65

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

☐ See Supplemental Box for further details.

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Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	9-12, 32-35	YES
	Claims	1-8, 13-31, 36-62	NO
Inventive step (IS)	Claims	NONE	YES
	Claims	1-62	NO
Industrial applicability (IA)	Claims	1-62	YES
	Claims	NONE	NO

2. Citations and explanations:

Claims 1-8, 13-31 and 36-62 lack novelty under PCT Article 33(2) as being anticipated by US 2009/0258865 A1 to Cartt et al. (hereinafter 'Cartt').

Regarding claim 1, Cartt teaches a pharmaceutical solution for nasal administration (para[0010]) consisting of:
(a) a benzodiazepine drug (para[0010]);
(b) one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof (para[0012]), in an amount from about 30% to about 95% (w/w) (para[0010], [0015]);
(c) one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w) (para[0010], [0016]); and (d) an alkyl glycoside (para[0019]), in a pharmaceutically-acceptable formulation for administration to one or more nasal mucosal membranes of a patient.

Regarding claim 2, Cartt teaches wherein the benzodiazepine drug is dissolved (para[0047]) in the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof (para[0047]), in an amount from about 30% to about 95% (w/w) (para[0010], [0015]); and the one or more alcohols or glycols, or any combinations thereof (para[0047]), in an amount from about 10% to about 70% (w/w) (para[0010], [0016]).

Regarding claim 3, Cartt teaches wherein the benzodiazepine drug is selected from the group consisting of: alprazolam (para[0011]).

Regarding claim 4, Cartt teaches wherein the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof (para[0011], [0196], [0199])).

Regarding claim 5, Cartt teaches containing about 1 to about 20 % (w/v) of benzodiazepine (para[0010], [0014], [0147], [0161], [0196]-[0204]).

Regarding 6, Cartt teaches containing about 1 to about 20 % (w/v) of diazepam (para[0010], [0014], [0147], [0161]).

Regarding claim 7, Cartt teaches wherein the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: alpha-tocopherol (para[0037]).

Regarding claim 8, Cartt teaches wherein the one or more alcohols are selected from the group consisting of: ethanol (para[0039]).

Regarding claim 13, Cartt teaches wherein the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from about 45% to about 85% (w/w) (para[0015]).

Regarding claim 14, Cartt teaches wherein the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from about 50% to about 75% (w/w) (para[0015]).

Regarding claim 15, Cartt teaches wherein the one or more alcohols or glycols, or any combinations thereof, is in an amount from about 15% to about 55% (w/w) (para[0015]).

Regarding claim 16, Cartt teaches wherein the one or more alcohols or glycols, or any combinations thereof, is in an amount from about 25% to about 40% (w/w) (para[0017]).

Regarding claim 17, Cartt teaches consisting of diazepam (5-15 % (w/v)) (para[0010], [0147],[0162], [0180], [0181], [0196]-[0200], Table 3 solution contains approx. 10% diazepam) , alkyl glycoside (0.01-1 % (w/v)) (para[0139]), vitamin E (45-65 % (w/v)) (para[0162]), ethanol (10-25 % (w/v)) (para[0016]-[0017], [0162])and benzyl alcohol (5-15 % (w/v) (para[0016]-[0017], [0162]).

----------continued in Supplemental Box----------

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
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Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Box No. V 2. Citations and explanations:

Regarding claim 18, Cartt teaches wherein the pharmaceutically-acceptable formulation comprises at least about 0.01 % (w/w) of an alkyl glycoside (para[0138], [0142]).

Regarding claim 19, Cartt teaches wherein the pharmaceutically-acceptable formulation about 0.01 % to 1 % (w/w) of an alkyl glycoside (para[0138], [0148]), such as dodecyl maltoside(para[0142]-[0143]).

Regarding claim 20, Cartt teaches consisting essentially of diazepam(para[0010], [0147],[0180], [0181], [0196]-[0200], vitamin E (para[0012], [0162]), ethanol (para[0016]-[0017], [0162]), benzyl alcohol (para[0016]-[0017], [0162]) and dodecyl maltoside (para[0142]-[0143]).

Regarding claim 21, Cartt teaches consisting of diazepam(para[0010], [0147],[0180], [0181], [0196]-[0200], vitamin E (para[0012], [0162]), ethanol (para[0016]-[0017], [0162]), benzyl alcohol (para[0016]-[0017], [0162]) and dodecyl maltoside (para[0142]-[0143]).

Regarding claim 22, Cartt teaches consisting of about 56.47% (w/v) vitamin E (para[0162]), about 10.5 % (w/v) benzyl alcohol (para[0162]), about 10 % (w/v) diazepam (para[0010], [0147],[0162][0180], [0181], [0196]-[0200], Table 3 solution 00 contains approx. 10% diazepam) about 0.25 % (w/v) dodecyl maltoside (para[0138], [0142]), q.s. dehydrated ethanol (para[0025], [0039], [0199]).

Regarding claim 23, Cartt teaches method of treating a patient with a disorder which may be treatable with a benzodiazepine drug (para[0003], [0020], [0050], [0194], [0214], comprising: administering to one or more nasal mucosal membranes of a patient a pharmaceutical solution for nasal administration consisting of a benzodiazepine drug (para[0010]), one or more natural or synthetic tocopherols or tocotrienols (para[0010]), or any combinations thereof, in an amount from about 30% to about 95% (w/w) (para[0010]); one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w) (para[0010]); and an alkyl glycoside (para[0019]).

Regarding claim 24, Cartt teaches wherein the benzodiazepine drug is dissolved (para[0047]) in the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof (para[0047]), in an amount from about 30% to about 95% (w/w) (para[0010], [0015]); and the one or more alcohols or glycols, or any combinations thereof (para[0047]), in an amount from about 10% to about 70% (w/w) (para[0010], [0016]).

Regarding claim 25, Cartt teaches wherein the natural or synthetic tocopherols or tocotrienols is Vitamin E (para[0012]).

Regarding claim 26, Cartt teaches wherein the benzodiazepine drug is selected from the group consisting of: alprazolam (para[0011]).

Regarding claim 27, Cartt teaches wherein the benzodiazepine drug is diazepam (para[011], [0147], [0180], [0181], [0196]-[0200]), or a pharmaceutically-acceptable salt thereof.

Regarding claim 28, Cartt teaches wherein the solution contains about 1 to about 20 % (w/v) of benzodiazepine (para[0010], [0014], [0147], [0161], [0196]-[0204], Table 3 solution 00 contains approx. 10% diazepam).

Regarding claim 29, Cartt teaches wherein the solution contains about 1 to about 20 % (w/v) of diazepam (para[0010], [0014], [0147], [0161], [0196]-[0204], Table 3 solution 00 contains approx. 10% diazepam).

Regarding claim 30, Cartt teaches wherein the one or more natural or synthetic tocopherols (para[0012]).

Regarding claim 31, Cartt teaches wherein the one or more alcohols are selected from the group consisting of: ethanol (para[0013]).

Regarding claim 36, Cartt teaches wherein the pharmaceutical solution comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 45% to about 85% (w/w) (para[0015]).

Regarding claim 37, Cartt teaches wherein the pharmaceutical solution comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 60% to about75% (w/w) (para[0015]).

Regarding claim 38, Cartt teaches wherein the pharmaceutical solution comprises one or more alcohols or glycols, or any combinations thereof, in an amount from about 15% to about 55% (w/w) (para[0016]).

Regarding claim 39, Cartt teaches wherein the pharmaceutical solution comprises one or more alcohols or glycols, or any combinations thereof, in an amount from about 25% to about 40% (w/w) (para[0017]).

Regarding claim 40, Cartt teaches wherein the solution contains ethanol (10-22.5 % (w/v)) (para[0016], [0017], [0023]) and benzyl alcohol (7.5-12.5 % (w/v) (para[0016], [0017], [0023]).

----------continued in Supplemental Box----------

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Prior Supplemental Box:

Regarding claim 41, Cartt teaches wherein the solution is in a pharmaceutically-acceptable spray formulation (para[0028]).

Regarding claim 42, Cartt teaches wherein the benzodiazepine is administered in a therapeutically effective amount from about 1 mg to about 20 mg (para[0028]).

Regarding claim 43, Cartt teaches wherein said pharmaceutical solution is in pharmaceutically-acceptable spray formulation (para[0028]) having volume from about 10 microL to about 200 microL (para[0028]).

Regarding claim 44, Cartt teaches wherein the administration of the pharmaceutical solution comprises spraying at least a portion of the therapeutically effective amount of the benzodiazepine into at least one nostril (para[0029]).

Regarding claim 45, Cartt teaches wherein the administration of the pharmaceutical solution comprises spraying at least a portion of the therapeutically effective amount of the benzodiazepine into each nostril (para[0029]).

Regarding claim 46, Cartt teaches wherein the administration of the pharmaceutical solution comprises spraying a first quantity of the pharmaceutical solution into the first nostril (para[0029]), spraying a second quantity of the pharmaceutical solution into a second nostril (para[0029]), and optionally after a pre-selected time delay, spraying a thirdquantity of the pharmaceutical solution into the first nostril (para[0029]).

Regarding claim 47, Cartt teaches further comprising, optionally after a pre-selected time delay, administering at least a fourth quantity of the pharmaceutical solution to the second nostril (para[0029]).

Regarding claim 48, Cartt teaches wherein nasal administration of the pharmaceutical solution begins at any time before or after onset of symptoms of a disorder which may be treatable with the pharmaceutical solution (para[0030]).

Regarding claim 49, Cartt teaches wherein the solution contains at least about 0.01% (w/w) of an alkyl glycoside (para[0138], [0142]).

Regarding claim 50, Cartt teaches wherein the solution contains about 0.01% to 1% (w/w) of an alkyl glycoside (para[0138], [0148]), such as dodecyl maltoside (para[0142]-[0143]).

Regarding claim 51, Cartt teaches the method of claim 50, wherein the solution contains about 0.01% to 1% (w/w) of dodecyl maltoside (para[0138], [0142]-[0143], [0148]).

Regarding claim 52, Cartt teaches wherein the solution consists essentially of diazepam (para[0010], [0147],[0180], [0181], [0196]-[0200], vitamin E (para[0012], [0162]), ethanol (para[0016]-[0017], [0162]), benzyl alcohol (para[0016]-[0017], [0162]) and dodecyl maltoside (para[0142]-[0143]).

Regarding claim 53, Cartt teaches wherein the solution consists of diazepam (para[0010], [0147],[0180], [0181], [0196]-[0200], vitamin E (para[0012], [0162]), ethanol (para[0016]-[0017], [0162]), benzyl alcohol (para[0016]-[0017], [0162]) and dodecyl maltoside (para[0142]-[0143]).

Regarding claim 54, Cartt teaches wherein the solution consists of about 56.47% (w/v) vitamin E (para[01162]), about 10.5% (w/v) benzyl alcohol (para[0162]), about 10 % (w/v) diazepam (para[0010], [0147],[0180], [0181], [0196]-[0200], Table 3 solution 00 contains approx. 10% diazepam) about 0.25 % (w/v) dodecyl maltoside (para[0138], [0142]), q.s. dehydrated ethanol (para[0025], [0039], [0199]).

Regarding claim 55, the method of one of claims 23-54 is taught. Cartt teaches wherein the solution consists of diazepam (para[0010], [0147],[0180], [0181], [0196]-[0200]), alkyl glycoside (para[0142]-[0143]), vitamin E (para[0162]), ethanol (para[0016]-[0017], [0162]), and benzyl alcohol (para[0016]-[0017], [0162]).

Regarding claim 56, the method of one of claims 23-54 is taught. Cartt teaches wherein the solution consists of diazepam (5-15 % (w/v))(para[0010], [0147],[0180], [0181], [0196]-[0200],Table 3 solution 00 contains approx. 10% diazepam) , alkyl glycoside (0.01-1 % (w/v)) (para[0138]), vitamin E (45-65% (w/v)) (para[0162]), ethanol (10-25 % (w/v)) (para[0016]-[0017], [0162]) and benzyl alcohol (5-15 % (w/v)) (para[0016]-[0017], [0162]).

Regarding claim 57, Cartt teaches consisting of diazepam (5-15% (w/v)) (para[0010], [0147],[0180], [0181], [0196]-[0200],Table 3 solution 00 contains approx. 10% diazepam), alkyl glycoside (0.01-1% (w/v)) (para[0138]), vitamin E (45-65 % (w/v)) (para[0162]), ethanol (10-25 % (w/v)) (para[0016]-[0017], [0162])and benzyl alcohol (5-15% (w/v) (para[0016]-[0017], [0162])).

Regarding claim 58, Cartt teaches consisting of diazepam (9-11% (w/v.(para[0010], [0147],[0180], [0181], [0196]-[0200]), dodecyl maltoside (0.1-0.5% (w/v)) (para (para[0138], [0142]-[0143]), vitamin E (50-60% (w/v (para[0162]), ethanol (15-22.5% (w/v (para[0016]-[0017], [0162]) and benzyl alcohol (7.5-12.5% (w/v) (para[0016]-[0017], [0162]).

----------continued in next Supplemental Box----------

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Prior Supplemental Box:

Regarding claim 59, Cartt teaches consisting of diazepam (10 % (w/v.(para[0010], [0147],[0180], [0181], [0196]-[0200]), dodecyl maltoside (0.15-0.3% (w/v)(para (para[0138], [0142]-[0143]), vitamin E (50-60 % (w/v)) (para[0162]), ethanol (17-20 % (w/v))(para[0016]-[0017], [0162]) and benzyl alcohol (10-12% (w/v)) (para[0016]-[0017], [0162]).

Regarding claim 60, Cartt teaches wherein the solution consists of diazepam (5-15% (w/v)) (para[0010], [0147],[0180], [0181], [0196]-[0200], Table 3 solution 00 contains approx. 10% diazepam), alkyl glycoside (0.01-1% (w/v)) (para[0138]), vitamin E (45-65% (w/v)) (para[0162]), ethanol (10-25% (w/v)) (para[0016]-[0017], [0162]) and benzyl alcohol (5-15% (w/v) (para[0016]-[0017], [0162])).

Regarding claim 61, Cartt teaches consisting of diazepam (9-11 % (w/v)) (para[0010], [0147],[0180], [0181], [0196]-[0200], Table 3 solution 00 contains approx. 10% diazepam) , dodecyl maltoside (0.1-0.5 % (w/v)) (para (para[0138], [0142]-[0143]), vitamin E (50-60% (w/v)) (para[0162]), ethanol (15-22.5% (w/v)) (para[0016]-[0017], [0162]) and benzyl alcohol (7.5-12.5% (w/v)) (para[0016]-[0017], [0162]).

Regarding claim 62, Cartt teaches consisting of diazepam (10% (w/v)) (para[0010], [0147],[0180], [0181], [0196]-[0200], Table 3 solution 00 contains approx. 10% diazepam), dodecyl maltoside (0.15-0.3 % (w/v)) (para[0138], [0142]-[0143]), vitamin E (50-60 % (w/v)) (para[0162]), ethanol (17-20% (w/v)) (para[0016]-[0017], [0162]) and benzyl alcohol (10-12 % (w/v)) (para[0016]-[0017], [0162]).

Claims 9-12 and 32-35 lack an inventive step under PCT Article 33(3) as being obvious over Cartt.

Regarding claim 9, Cartt teaches the composition containing one or more alcohols (para[0013]), but does not specifically teach two or more alcohols. It would have been obvious to one of ordinary skill in the art that the embodiment wherein the composition of Cartt contained two or more alcohols was encompassed in the teaching of "or more alcohols" and "combinations thereof" that Cartt teaches (para[0013]).

Regarding claim 10, Cartt teaches aspects of containing ethanol (1-25% (w/v)) (para[0016]-[0017]) and benzyl alcohol (1-25 % (w/v)) (para[0016]-[0017]), in that Cartt teaches one or more and a combination thereof of alcohols and teaches benzyl alcohol (para[0023] and ethanol (para[0023]). It would have been obvious to one of ordinary skill in the art to combine alcohols such as benzyl alcohol and ethanol and to determine the specific amount of each ingredient to add because Cartt teaches between 10-70% alcohols and glycols (para[0016]. One of ordinary skill in the art would have been motivated to use any combination of each alcohol such as those claimed based on the teaching of Cartt (para[0016]) and the exact amounts would have been obvious to one of ordinary skill in the art as determined through routine experimentation.

Regarding claim 11, Cartt teaches aspects of containing ethanol (10-22.5 % (w/v)) and benzyl alcohol (7.5-12.5% (w/v)) (para[0016]-[0017].in that Cartt teaches one or more and a combination thereof of alcohols and teaches benzyl alcohol (para[0023] and ethanol (para[0023]). It would have been obvious to one of ordinary skill in the art to combine alcohols such as benzyl alcohol and ethanol and to determine the specific amount of each ingredient to add because Cartt teaches between 10-70% alcohols and glycols (para[0016]. One of ordinary skill in the art would have been motivated to use any combination of each alcohol such as those claimed based on the teaching of Cartt (para[0016]) and the exact amounts would have been obvious to one of ordinary skill in the art as determined through routine experimentation.

Regarding claim 12, Cartt teaches wherein the benzodiazepine is present in the pharmaceutical solution in a concentration from about 20 mg/mL to about 200 mg/mL (para[0014]).

Regarding claim 32, Cartt teaches aspects of wherein the solution contains two or more alcohols, in that Cartt teaches one or more alcohols and a combination thereof (para[0013]). It would have been obvious to one of ordinary skill in the art that the embodiment wherein the composition of Cartt contained two or more alcohols was encompassed in the teaching of "or more alcohols" and "combinations thereof" that Cartt teaches (para[0013]).

Regarding claim 33, Cartt teaches aspects of wherein the solution contains ethanol (1-25 % (w/v)) (para[0016]-[0017]) and benzyl alcohol (1-25 % (w/v)) (para[0016]-[0017]), in that Cartt teaches one or more and a combination thereof of alcohols and teaches benzyl alcohol (para[0023] and ethanol (para[0023]). It would have been obvious to one of ordinary skill in the art to combine alcohols such as benzyl alcohol and ethanol and to determine the specific amount of each ingredient to add because Cartt teaches between 10-70% alcohols and glycols (para[0016]. One of ordinary skill in the art would have been motivated to use any combination of each alcohol such as those claimed based on the teaching of Cartt (para[0016]) and the exact amounts would have been obvious to one of ordinary skill in the art as determined through routine experimentation.

Regarding claim 34, Cartt teaches wherein the benzodiazepine drug is present in the pharmaceutical solution in a concentration of from about 10 mg/mL to about 250 mg/mL (para[0014]).

Regarding claim 35, Cartt teaches wherein the benzodiazepine drug is present in the pharmaceutical solution in a concentration of from about 20 mg/mL to about 50 mg/mL (para[0014]).

Claims 1-62 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(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, CL, 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, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report (Art. 21(3))*

(88) Date of publication of the international search report:
1 May 2014

(54) Title: ADMINISTRATION OF BENZODIAZEPINE

(57) Abstract: The invention relates to pharmaceutical compositions comprising one or more benzodiazepine drugs for nasal administration, methods for producing and for using such compositions.

WO 2012/174158 A3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/42311

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 43/62; A61K 31/55 (2012.01)
USPC - 514/220-221
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC-514/220-221

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC-424/400, 434 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PUBWEST, Google Scholar, Google, Intranasal, nasal, inhalation, mucosal, drug, delivery, denzodazepine, diazepam, tocopherol, tocotrienol, Vitamin E, alcohol, ethanol, benzyl alcohol, alkyl glycoside

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2009/0258865 A1 (Cartt et al.) 15 October 2009 (15.10.2009) para [0010]-[0021], [0024]-[0030], [0035]-[0039], [0047], [0138], [0142]-[0143], [0147], [0161]-[0162], [0180]-[0181], [0196]-[0204]	1-62
A	US 2009/0130216 A1 (Cartt et al.) 21 May 2009 (21.05.2009) entire document	1-62
A	US 2008/0279784 A1 (Cartt et al.) 13 November 2008 (13.11.2008) entire document	1-62
A	US 2009/0304801 A1 (Liversidge et al.) 10 December 2009 (10.12.2009) entire document	1-62

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 August 2012 (10.08.2012)	31 AUG 2012
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/42311

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 63-65
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

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Date
12.05.14

Reference	Application No./Patent No.
EPA-124 519	12801372.9 - 1453 / 2720699 PCT/US2012042311
Applicant/Proprietor	
Hale BioPharma Ventures, LLC	

Communication pursuant to Rules 161(2) and 162 EPC

1. Amendment of the application (R. 161(2) EPC)

The above-mentioned international (Euro-PCT) application has entered the European phase.

Under Articles 28, 41 PCT and Rules 52, 78 PCT the application may be amended before a designated or elected Office.

In accordance with Rule 161(2) EPC, you may amend your application once within a **non-extendable period of six months** after notification of the present communication.

If filing amendments, you must identify them and indicate the basis for them in the application as filed. Failure to meet either requirement may lead to a communication from the Examining Division requesting that you correct this deficiency (R. 137(4) EPC).

The claims applicable on expiry of this period, i.e. those filed on entry into the European phase or in response to the present communication, will form the basis for the calculation of any claims fee to be paid (see page 2).

--2/

2 Claims fees under Rule 162 EPC

If the application documents on which the European grant procedure is to be based comprise more than fifteen claims, a claims fee shall be payable for the sixteenth and each subsequent claim within the period provided for in Rule 159(1) EPC.

☐ Based on the application documents currently on file, all necessary claims fees have already been paid (or the documents do not comprise more than 15 claims).

☐ All necessary fees will be/have been debited automatically according to the automatic debit order.

☑ The claims fees due for the claims 16 to 65 were not paid within the above-mentioned period.

Any outstanding claims fee, either based on the current set of claims or on any amended claims to be filed pursuant to Rule 161 EPC (see page 1), may still be validly paid within a **non-extendable period of six months** after notification of this communication (R. 162(2) EPC).

If a payment is made for only some of the claims, you must indicate for which claims it is intended. If a claims fee is not paid in due time, the claim concerned is deemed to be abandoned (R. 162(4) EPC).

If claims fees have already been paid, but on expiry of the above-mentioned period there is a new set of claims containing fewer fee-incurring claims than before, the claims fees in excess of those due under Rule 162(2), second sentence EPC will be refunded (R. 162(3) EPC).

You are reminded that the supplementary search carried out according to Article 153(7) EPC will relate only to the last set of claims applicable on expiry of the above period AND will be confined to those fee-incurring claims for which fees have been paid in due time.

The claims fee is currently

EUR 235 for the 16th and each subsequent claim up to the limit of 50
EUR 580 for the 51st and each subsequent claim

Note to users of the automatic debiting procedure
Unless the EPO receives prior instructions to the contrary, the fees for all claims incurring fees will be debited on the last day of the period for payment. For further details see the Arrangements for the automatic debiting procedure, Supplementary publication 4 - OJ EPO 2014.

Important information concerning fee amounts
Following any amendment to the Rules relating to Fees, the amount(s) mentioned in this communication may be different from the amount(s) **actually due on the date of payment.** The latest version of the Schedule of fees and expenses, published as a Supplement to the Official Journal of the EPO, is also available on the EPO website (**www.epo.org**) and can be found under **www.epo.org/schedule-of-fees**, which allows the viewing, downloading and searching for individual fee amounts, both current and previous.
Please note that procedural fees are usually adjusted every two years, on even years, with effect from 1 April.

Payments by cheque delivered or sent direct to the EPO are no longer accepted as from 1 April 2008 (see OJ EPO 2007, 626).

Receiving Section

WUESTHOFF & WUESTHOFF

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13 November 2014

European Patent Application 12 801 372.9-1453 based on PCT/US2012/042311
Title: Administration of benzodiazepine
Applicant: Hale BioPharma Ventures, LLC
Our ref.: EPA-124 519

In response to the Communication pursuant to Rules 161(2) and 162 EPC dated 12 May 2014:

We herewith file a revised set of claims 1-15. To assist the Examiner, the support for the amendments is indicated in the following (see also the marked-up version of the claims):

Amended claim 1 is based on original PCT claim 1 and e.g. paragraphs [010] and [011] of the specification (defining the use of a combination of ethanol and benzyl alcohol).

Claims 2-13 are based on the original PCT claims as indicated in the marked-up copy, wherein some formal amendments have been performed.

Claim 14 is based on original PCT claim 23 and is further supported by e.g. paragraphs [010] and [011] of the specification (defining the use of a combination of ethanol and benzyl alcohol). In addition, claim 14 has been reworded to comply with the second medical use claim format.

Claim 15 is based on e.g. paragraph [011] of the specification (last lines on page 4).

Dr. Hendrik Wichmann
European Patent Attorney

Enclosures:
Amended set of claims 1-15 (marked-up version and clean copy)

CLAIMS

1. A pharmaceutical solution for nasal administration consisting of:

(a) a benzodiazepine drug;

(b) one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w);

(c) ~~one or more alcohols or glycols, or any combinations thereof~~ethanol and benzyl alcohol, in ~~an~~ a combined amount from about 10% to about 70% (w/w); and

(d) an alkyl glycoside~~,~~

~~in a pharmaceutically-acceptable formulation for administration to one or more nasal mucosal membranes of a patient~~.

~~2. The pharmaceutical solution of claim 1, wherein the benzodiazepine drug is dissolved in the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); and the one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w).~~

~~3~~2. The pharmaceutical solution of claim ~~2~~1, wherein the benzodiazepine drug is selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, any pharmaceutically-acceptable salts thereof, and any combinations thereof.

~~4~~3. The pharmaceutical solution of claim ~~3~~2, wherein the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof.

~~5~~4. The pharmaceutical solution of claim 1, containing about 1 to about 20 % (w/v) of benzodiazepine.

~~6~~5. The pharmaceutical solution of claim ~~5~~4, containing about 1 to about 20 % (w/v) of diazepam.

~~7~~6. The pharmaceutical solution of claim 1, wherein the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β- tocotrienol, γ- tocotrienol, δ- tocotrienol, tocophersolan, any isomers thereof, any esters thereof, any analogs or derivatives thereof, and any combinations thereof.

~~8. The pharmaceutical solution of claim 1, wherein the one or more alcohols are selected from the group consisting of: ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, or any combinations thereof.~~

~~9. The pharmaceutical solution of claim 1, containing two or more alcohols.~~

~~10~~7. The pharmaceutical solution of claim 1, containing 1-25 % (w/v) ethanol ~~(1-25 % (w/v))~~ and 1-25 % (w/v) benzyl alcohol ~~(1-25 % (w/v))~~.

~~11~~8. The pharmaceutical solution of claim 1, containing 10-22.5 % (w/v) ethanol ~~(10-22.5 % (w/v))~~ and 7.5-12.5 % (w/v) benzyl alcohol ~~(7.5-12.5 % (w/v))~~.

~~12. The pharmaceutical solution of claim 11, wherein the benzodiazepine is present in the pharmaceutical solution in a concentration from about 20 mg/mL to about 200 mg/mL.~~

~~13~~9. The pharmaceutical solution of claim 1, wherein the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from about 45% to about 85% (w/w).

~~14. The pharmaceutical solution of claim 13, wherein the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from about 50% to about 75% (w/w).~~

~~15. The pharmaceutical solution of claim 1, wherein the one or more alcohols or glycols, or any combinations thereof, is in an amount from about 15% to about 55% (w/w).~~

~~16. The pharmaceutical solution of claim 15, wherein the one or more alcohols or glycols, or any combinations thereof, is in an amount from about 25% to about 40% (w/w).~~

~~17~~10. The solution of claim 1, consisting of 5-15 % (w/v) diazepam ~~(5-15 % (w/v))~~, 0.01-1 % (w/v) alkyl glycoside ~~(0.01-1 % (w/v))~~, 45-65 % (w/v) vitamin E ~~(45-65 % (w/v))~~, 10-25 % (w/v) ethanol ~~(10-25 % (w/v))~~ and 5-15 % (w/v) benzyl alcohol ~~(5-15 % (w/v))~~.

~~18~~11. The solution of claim 1, wherein the pharmaceutically-acceptable formulation comprises at least about 0.01% (w/w) of an alkyl glycoside.

~~19~~12. The solution of claim ~~18~~11, wherein the pharmaceutically-acceptable formulation comprises about 0.01% to 1% (w/w) of ~~an alkyl glycoside, such as~~ dodecyl maltoside.

~~20~~13. The solution of claim 1, consisting essentially of diazepam, vitamin E, ethanol, benzyl alcohol and dodecyl maltoside.

~~21. The solution of claim 20, consisting of diazepam, vitamin E, ethanol, benzyl alcohol and dodecyl maltoside.~~

~~22. The solution of claim 21, consisting of about 56.47% (w/v) vitamin E, about 10.5 % (w/v) benzyl alcohol, about 10 % (w/v) diazepam, about 0.25 % (w/v) dodecyl maltoside, q.s. dehydrated ethanol.~~

~~23~~14. A ~~method~~solution of one of claims 1-13 for use in intranasal administration for treatment of ~~treating~~ a patient with a disorder which may be treatable with a benzodiazepine drug~~, comprising: administering to one or more nasal mucosal membranes of a patient a pharmaceutical solution for nasal administration consisting of a benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w); and an alkyl glycoside~~.

~~24. The method of claim 23, wherein the benzodiazepine drug is dissolved in the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); and the one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w).~~

~~25. The method of claim 24, wherein the natural or synthetic tocopherols or tocotrienols is Vitamin E.~~

~~26. The method of claim 23, wherein the benzodiazepine drug is selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, or any pharmaceutically-acceptable salts thereof, and any combinations thereof.~~

~~27. The method of claim 26, wherein the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof.~~

~~28. The method of claim 23, wherein the solution contains about 1 to about 20 % (w/v) of benzodiazepine.~~

~~29. The method of claim 28, wherein the solution contains about 1 to about 20 % (w/v) of diazepam.~~

~~30. The method of claim 23, wherein the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ-tocotrienol, δ-tocotrienol, tocophersolan, any isomers thereof, any esters thereof, any analogs or derivatives thereof, and any combinations thereof.~~

~~31. The method of claim 23, wherein the one or more alcohols are selected from the group consisting of: ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, and any combinations thereof.~~

~~32. The method of claim 23, wherein the solution contains two or more alcohols.~~

~~33. The method of claim 23, wherein the solution contains ethanol (1-25 % (w/v)) and benzyl alcohol (1-25 % (w/v)).~~

~~34. The method of claim 33, wherein the benzodiazepine drug is present in the pharmaceutical solution in a concentration of from about 10 mg/mL to about 250 mg/mL.~~

~~35. The method of claim 34, wherein the benzodiazepine drug is present in the pharmaceutical solution in a concentration of from about 20 mg/mL to about 50 mg/mL.~~

~~36. The method of claim 23, wherein the pharmaceutical solution comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 45% to about 85% (w/w).~~

~~37. The method claim 36, wherein the pharmaceutical solution comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 60% to about 75% (w/w).~~

~~38. The method of claim 23, wherein the pharmaceutical solution comprises one or more alcohols or glycols, or any combinations thereof, in an amount from about 15% to about 55% (w/w).~~

~~39. The method of claim 38, wherein the pharmaceutical solution comprises one or more alcohols or glycols, or any combinations thereof, in an amount from about 25% to about 40% (w/w).~~

~~40. The method of claim 23, wherein the solution contains ethanol (10-22.5 % (w/v)) and benzyl alcohol (7.5-12.5 % (w/v)).~~

~~41. The method of claim 23, wherein the solution is in a pharmaceutically acceptable spray formulation.~~

~~42. The method of claim 41, wherein the benzodiazepine is administered in a therapeutically effective amount from about 1 mg to about 20 mg.~~

~~43. The method of claim 42, wherein said pharmaceutical solution is in a pharmaceutically acceptable spray formulation having volume from about 10 µL to about 200 µL.~~

~~44. The method of claim 43, wherein the administration of the pharmaceutical solution comprises spraying at least a portion of the therapeutically effective amount of the benzodiazepine into at least one nostril.~~

~~45. The method of claim 43, wherein the administration of the pharmaceutical solution comprises spraying at least a portion of the therapeutically effective amount of the benzodiazepine into each nostril.~~

~~46. The method of claim 45, wherein the administration of the pharmaceutical solution comprises spraying a first quantity of the pharmaceutical solution into the first nostril, spraying a second quantity of the pharmaceutical solution into a second nostril, and optionally after a pre-selected time delay, spraying a third quantity of the pharmaceutical solution into the first nostril.~~

~~47. The method of claim 46, further comprising, optionally after a pre-selected time delay, administering at least a fourth quantity of the pharmaceutical solution to the second nostril.~~

~~48. The method of claim 46, wherein nasal administration of the pharmaceutical solution begins at any time before or after onset of symptoms of a disorder which may be treatable with the pharmaceutical solution.~~

~~49. The method of claim 23, wherein the solution contains at least about 0.01% (w/w) of an alkyl glycoside.~~

~~50. The method of claim 24, wherein the solution contains about 0.01% to 1% (w/w) of an alkyl glycoside.~~

~~51. The method of claim 50, wherein the solution contains about 0.01% to 1% (w/w) of dodecyl maltoside.~~

~~52. The method of claim 23, wherein the solution consists essentially of diazepam, vitamin E, ethanol, benzyl alcohol and dodecyl maltoside.~~

~~53. The method of claim 23, wherein the solution consists of diazepam, vitamin E, ethanol, benzyl alcohol and dodecyl maltoside.~~

~~54. The method of claim 23, wherein the solution consists of about 56.47% (w/v) vitamin E, about 10.5 % (w/v) benzyl alcohol, about 10 % (w/v) diazepam, about 0.25 % (w/v) dodecyl maltoside, q.s. dehydrated ethanol.~~

~~55. The method of one of claims 23-54, wherein the solution consists of diazepam, alkyl glycoside, vitamin E, ethanol, and benzyl alcohol.~~

~~56. The method of one of claims 23-54, wherein the solution consists of diazepam (5-15 % (w/v)), dodecyl maltoside (0.01-1 % (w/v)), vitamin E (45-65 % (w/v)), ethanol (10-25 % (w/v)) and benzyl alcohol (5-15 % (w/v)).~~

~~57. The solution of claim 17, consisting of diazepam (5-15 % (w/v)), dodecyl maltoside (0.01-1 % (w/v)), vitamin E (45-65 % (w/v)), ethanol (10-25 % (w/v)) and benzyl alcohol (5-15 % (w/v)).~~

~~58. The solution of claim 17, consisting of diazepam (9-11 % (w/v)), dodecyl maltoside (0.1-0.5 % (w/v)), vitamin E (50-60 % (w/v)), ethanol (15-22.5 % (w/v)) and benzyl alcohol (7.5-12.5 % (w/v)).~~

~~59. The solution of claim 17, consisting of diazepam (10 % (w/v)), dodecyl maltoside (0.15-0.3 % (w/v)), vitamin E (50-60 % (w/v)), ethanol (17-20 % (w/v)) and benzyl alcohol (10-12 % (w/v)).~~

~~60. The method of claim 23, wherein the solution consists of diazepam (5-15 % (w/v)), dodecyl maltoside (0.01-1 % (w/v)), vitamin E (45-65 % (w/v)), ethanol (10-25 % (w/v)) and benzyl alcohol (5-15 % (w/v)).~~

~~61. The method of claim 23, wherein the solution consists of diazepam (9-11 % (w/v)), dodecyl maltoside (0.1-0.5 % (w/v)), vitamin E (50-60 % (w/v)), ethanol (15-22.5 % (w/v)) and benzyl alcohol (7.5-12.5 % (w/v)).~~

~~62. The method of claim 23, wherein the solution consists of diazepam (10 % (w/v)), dodecyl maltoside (0.15-0.3 % (w/v)), vitamin E (50-60 % (w/v)), ethanol (17-20 % (w/v)) and benzyl alcohol (10-12 % (w/v)).~~

~~63. The method of one of claims 23-56 or 60-62, wherein said treatment achieves bioavailability that is from about 80-125% of that achieved with the same benzodiazepine administered intravenously.~~

~~64. The method of claim 63, wherein said treatment achieves bioavailability that is from about 90-110% of that achieved with the same benzodiazepine administered intravenously.~~

~~65. The method of claim 64, wherein said treatment achieves bioavailability that is from about 92.5 to 107.5% that obtained with the same benzodiazepine administered intravenously.~~15. The solution for use according to claim 14, wherein the disorder is seizure.

CLAIMS

1. A pharmaceutical solution for nasal administration consisting of:

(a) a benzodiazepine drug;

(b) one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w);

(c) ethanol and benzyl alcohol, in a combined amount from about 10% to about 70% (w/w); and

(d) an alkyl glycoside.

2. The pharmaceutical solution of claim 1, wherein the benzodiazepine drug is selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, any pharmaceutically-acceptable salts thereof, and any combinations thereof.

3. The pharmaceutical solution of claim 2, wherein the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof.

4. The pharmaceutical solution of claim 1, containing about 1 to about 20 % (w/v) of benzodiazepine.

5. The pharmaceutical solution of claim 4, containing about 1 to about 20 % (w/v) of diazepam.

6. The pharmaceutical solution of claim 1, wherein the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β- tocotrienol, γ- tocotrienol, δ- tocotrienol, tocophersolan, any isomers thereof, any esters thereof, any analogs or derivatives thereof, and any combinations thereof.

7. The pharmaceutical solution of claim 1, containing 1-25 % (w/v) ethanol and 1-25 % (w/v) benzyl alcohol.

8. The pharmaceutical solution of claim 1, containing 10-22.5 % (w/v) ethanol and 7.5-12.5 % (w/v) benzyl alcohol.

9. The pharmaceutical solution of claim 1, wherein the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from about 45% to about 85% (w/w).

10. The solution of claim 1, consisting of 5-15 % (w/v) diazepam, 0.01-1 % (w/v) alkyl glycoside, 45-65 % (w/v) vitamin E, 10-25 % (w/v) ethanol and 5-15 % (w/v) benzyl alcohol.

11. The solution of claim 1, wherein the pharmaceutically-acceptable formulation comprises at least about 0.01% (w/w) of an alkyl glycoside.

12. The solution of claim 11, wherein the pharmaceutically-acceptable formulation comprises about 0.01% to 1% (w/w) of dodecyl maltoside.

13. The solution of claim 1, consisting essentially of diazepam, vitamin E, ethanol, benzyl alcohol and dodecyl maltoside.

14. A solution of one of claims 1-13 for use in intranasal administration for treatment of a patient with a disorder which may be treatable with a benzodiazepine drug.

15. The solution for use according to claim 14, wherein the disorder is seizure.

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Application No.: 12801372.9

The search has started on 10.03.15 (see Notice from the European Patent Office dated 03/2013, OJ EPO 2013, 153).

Receiving Section

Europäisches Patentamt
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SUPPLEMENTARY EUROPEAN SEARCH REPORT

Application Number
EP 12 80 1372

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
A	WO 2009/120933 A2 (PARTICLE SCIENCES INC [US]) 1 October 2009 (2009-10-01) * page 4, line 13 - page 10, line 2 * * claims 1-13 * -----	1-15	INV. A61K9/08 A61K47/10 A61K47/22 A61K47/26
A,D	US 2009/047347 A1 (MAGGIO EDWARD T [US]) 19 February 2009 (2009-02-19) * the whole document * -----	1-15	A61K31/5513 A61K31/355 A61K45/06 A61P25/08
A	WO 03/004015 A1 (WEST PHARM SERV DRUG RES LTD [GB]) 16 January 2003 (2003-01-16) * the whole document * -----	1-15	
A	WO 95/31217 A1 (DUMEX LTD AS [DK]) 23 November 1995 (1995-11-23) * page 6, paragraph 6 - page 13, paragraph 1 * * page 14 - page 16; examples 1,2 * * page 20 - page 22; examples 8-11 * * page 24 - page 25; examples 17,19 * * claims 1-25 * -----	1-15	
			TECHNICAL FIELDS SEARCHED (IPC)
A	DATABASE WPI Section Ch, Week 200164 Thomson Scientific, London, GB; Class B02, AN 2001-566115 XP002737233, SUN L; WANG W; YANG P: "Nasal spray for curing status epilepticus (SE) and epilepsy, comprises alprazolam and carriers", -& CN 1 303 674 A ((SHAN-N) SHANDONG PROV MEDICAL IND INST) 18 July 2001 (2001-07-18) * the whole document * -----	1-15	A61K

The supplementary search report has been based on the last set of claims valid and available at the start of the search.

Place of search	Date of completion of the search	Examiner
The Hague	18 March 2015	Gómez Gallardo, S

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C04)

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 12 80 1372

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

18-03-2015

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2009120933 A2	01-10-2009	CN 101998828 A	30-03-2011
		EP 2271214 A2	12-01-2011
		US 2011038899 A1	17-02-2011
		WO 2009120933 A2	01-10-2009
US 2009047347 A1	19-02-2009	NONE	
WO 03004015 A1	16-01-2003	NONE	
WO 9531217 A1	23-11-1995	AT 223232 T	15-09-2002
		AU 697540 B2	08-10-1998
		CA 2189328 A1	23-11-1995
		DE 69528057 D1	10-10-2002
		DE 69528057 T2	06-11-2003
		DK 0762896 T3	06-01-2003
		EP 0762896 A1	19-03-1997
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		FI 964583 A	15-11-1996
		NO 964832 A	13-01-1997
		NZ 287857 A	24-09-1998
		PT 762896 E	31-01-2003
		US 6193985 B1	27-02-2001
		WO 9531217 A1	23-11-1995
CN 1303674 A	18-07-2001	NONE	

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

The examination is being carried out on the **following application documents**

Description, Pages

1-65	as published

Claims, Numbers

1-15	received on	14-11-2014	with letter of	13-11-2014

Drawings, Sheets

1/5-5/5	as published

1. CITED DOCUMENT

Reference is made to the following document; the numbering will be adhered to in the rest of the procedure.

D6 US 2009/258865 A1 (HALE BIOPHARMA VENTURES LLC [US]) 15 October 2009 (2009-10-15); cited in the International Search Report

2. AMENDMENTS (Art. 123(2) EPC)

The amendments filed with letter of 13-11-2014 do not contravene the requirements of Article 123(2) EPC.

3. CLARITY (Art. 84 EPC)

The use of the term "*about*", in claims 1, 4, 5, 9, 11 and 12, is indefinite and as such renders the scope of said claims unclear (Art. 84 EPC). This objection can only be overcome by deleting this term from the concerned claims. For the assessment of novelty, this term is construed in its broadest possible meaning.

4. NOVELTY (Art. 54 EPC)

The present application does not meet the requirements of Article 52(1) EPC because the subject-matter of claims 1-6, 9, 11, 14 and 15 is not new within the meaning of Article 54(1) and (2) EPC.

Document D6 originates from the same applicant. He should, thus, be perfectly aware of its contents. This document discloses (cf. the whole document) an intranasal solution consisting of (a) a benzodiazepine drug (preferably diazepam), (b) one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount of 30-95% (w/w), (c) one or more alcohols or glycols, or any combinations thereof, in an amount of 10-70% (w/w), and (d) optionally one or more alkyl glycosides. The one or more alcohols are selected from the group consisting of ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, or any combinations thereof (the combination of ethanol and benzyl alcohol being thus one of the possible combinations). The above solution is used for treating a patient with a disorder that may be treatable with a benzodiazepine drug, more particularly in the treatment of seizures. Therefore, the subject-matter of claims 1-6, 9, 11, 14 and 15 is not new in view of D6.

5. INVENTIVE STEP (Art. 56 EPC)

5.1. Should the applicant restore novelty of the above-mentioned claims 1-6, 9, 11, 14 and 15, document D6 should be taken into consideration as it seems to be of particular relevance as far as inventive step is concerned (Art. 56 EPC).

5.2. Document D6 (cf. above) can be considered to be the closest prior art to the subject-matter of claim 7.

The subject-matter of claim 7 differs from D6 in that the solution comprises 1-25 % (w/v) of ethanol and 1-25 % (w/v) of benzyl alcohol.

No unexpected effect whatsoever has been demonstrated in the application for the selection of the claimed individual amounts of ethanol and benzyl alcohol.

The objective technical problem to be solved by the present application may therefore be regarded as the provision of an alternative solution for nasal administration consisting of (a) a benzodiazepine drug, (b) one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount of 30-95% (w/w), (c) a combination of ethanol and benzyl alcohol, in an amount of 10-70% (w/w), and (d) one or more alkyl glycosides.

The solution proposed in claim 7 cannot be considered to be inventive because, in the absence of any unexpected effect associated therewith, the person skilled in the art would consider adjusting the amounts of ethanol and benzyl alcohol by mere routine experimentation and, by doing so, would inevitably arrive at the claimed amounts, without exercising inventive skill (Art. 56 EPC). The same argument applies *mutatis mutandis* to the subject-matter of claim 8, which refers to the amounts 10-22.5 % (w/v) and 7.5-12.5 % (w/v) of ethanol and benzyl alcohol, respectively (Art. 56 EPC).

5.3. Document D6 (cf. above) can also be considered to be the closest prior art to the subject-matter of claim 10.

The subject-matter of claim 10 differs from D6 in that the amounts of ethanol and benzyl alcohol in the solution are 10-25 % (w/v) and 5-15 % (w/v), respectively. The claimed amounts of diazepam, alkyl glycoside and vitamin E are all known from D6. The same argument given for claims 7 and 8 applies, therefore, *mutatis mutandis* to the subject-matter of claim 10, which cannot be considered inventive either (Art. 56 EPC).

5.4. Document D6 (cf. above) can also be considered to be the closest prior art to the subject-matter of claims 12 and 13.

The subject-matter of claims 12 and 13 differs from D6 in that the alkyl glycoside is dodecyl maltoside.

No unexpected effect whatsoever has been demonstrated in the application for the selection of this specific alkyl glycoside.

The objective technical problem to be solved by the present application may therefore be regarded as the provision of an alternative solution for nasal administration consisting of (a) a benzodiazepine drug, (b) one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount of 30-95% (w/w), (c) a combination of ethanol and benzyl alcohol, in an amount of 10-70% (w/w), and (d) one or more alkyl glycosides.

Dodecyl maltoside is one of the alkyl glycosides listed in D6. It would, therefore, be obvious for the skilled person to select dodecyl maltoside as the alkyl glycoside of the nasal solution. No inventive step can, therefore, be acknowledged for claims 12 and 13 (Art. 56 EPC).

6. CLARITY (Art. 84 EPC)

6.1. The term "*derivatives*", in claim 6, renders its scope unclear, since it is not known to the skilled reader which structures are intended to be encompassed by this term. This term includes compounds obtained from another compound by a chemical reaction (including compounds which are structurally remote from the starting material), functional derivatives (such as compounds wherein hetero-atoms are exchanged by alternative atoms), compounds with numerous different types of side groups, etc. Support within the meaning of Art. 84 EPC is to be found, however, only for those compounds that are specifically claimed. This objection can only be overcome by deleting the term "*derivatives*" from claim 6.

6.2. Claim 13 depends on claim 1 and refers to the solution consisting essentially of diazepam, vitamin E, ethanol, benzyl alcohol and dodecyl maltoside. The term "consisting essentially of" allows for other components to be present in the solution, which would be in contradiction with the subject-matter of claim 1, referring to a solution that consists (exclusively) of a benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, a combination of ethanol and benzyl alcohol, and an alkyl glycoside (wherein other components are excluded from the solution) (Art. 84 EPC). This objection can only be overcome by replacing the term "consisting essentially of" by "consisting of" in claim 13.

7. CONCLUSIONS

7.1. Should the applicant render the subject-matter of the present application novel by pointing out the importance of a technical feature that is not described explicitly in the prior art or by introducing into the claims the use of a specific ingredient or a specific amount or whatever, an inventive step may only be recognized if he demonstrates that a surprising and/or synergistic effect (with support of experimental data comparing the properties of present and prior art compositions) is attributed to the distinguishing technical feature that the skilled man in the art will not be able to deduct from the prior art. In the absence of a surprising effect directly attributed to the distinguishing feature or evidence of a particular prejudice, an inventive step cannot be acknowledged

because the introduced/distinguishing technical feature will be considered as an obvious or arbitrary alternative that the skilled man in the art will perform by routine (Art. 56 EPC).

7.2. When filing amended claims, the applicant should at the same time bring the description into conformity with the amended claims. Care should be taken during revision, especially of the introductory portion and any statements of problem or advantage, not to add subject-matter which extends beyond the content of the application as originally filed (Art. 123(2) EPC).

7.3. In order to facilitate the examination of the conformity of the amended application with the requirements of Article 123(2) EPC, the applicant is requested to clearly identify the amendments carried out, irrespective of whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based.

WUESTHOFF & WUESTHOFF

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Europäisches Patentamt
- Herrn Benoît Battistelli
Präsident -

80298 München

26. März 2015

Wuesthoff & Wuesthoff ist jetzt eine Partnerschaftsgesellschaft mit beschränkter Berufshaftung

Sehr geehrter Herr Präsident Battistelli,

die Rechtsform unserer Kanzlei hat sich in eine Partnerschaftsgesellschaft mit beschränkter Berufshaftung (PartG mbB) geändert. Wir sind jetzt im Partnerschaftsregister am Amtsgericht München unter der Nummer PR 1403 eingetragen und führen jetzt den Namen "Wuesthoff & Wuesthoff Patentanwälte PartG mbB".

Sollten Sie Fragen haben, können Sie sich gerne an uns wenden.

Mit freundlichen Grüßen

Dr. Jobst Wibbelmann
(Geschäftsführender Partner)

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European Patent Office
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European Patent Office
80298 MUNICH
GERMANY

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81541 München
ALLEMAGNE

Date
26.03.15

Reference	Application No./Patent No.
EPA-124 519	12801372.9 - 1455 / 2720699 PCT/US2012042311
Applicant/Proprietor	
Hale BioPharma Ventures, LLC	

Communication

The extended European search report is enclosed.

The extended European search report includes, pursuant to Rule 62 EPC, the supplementary European search report (Art. 153(7) EPC) and the European search opinion.

Copies of documents cited in the European search report are attached.

☑ 0 additional set(s) of copies of such documents is (are) enclosed as well.

Refund of the search fee
If applicable under Article 9 Rules relating to fees, a separate communication from the Receiving Section on the refund of the search fee will be sent later.

Should you wish to further prosecute this application in the examination phase, your attention is drawn to the provisions of Rule 70a EPC. An invitation to respond to the extended European search report will be issued shortly (R. 70(2) EPC).

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12801372.9 - 1455 / 2720699 30.03.15

Client Database System (CDS) - clean up.

Application Nr.: 12801372.9

Following clean up action in CDS the entries concerning the **Representative for the applicant** have been amended and are now as follows:

Wichmann, Hendrik
Wuesthoff & Wuesthoff
Patentanwälte PartG mbB
Schweigerstraße 2
81541 München
DE

Where appropriate, the European Patent Register at www.epo.org/register will be updated to show the amended details.

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Wichmann, Hendrik
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Date
13.04.15

Reference	Application No./Patent No.
EPA-124 519	12801372.9 - 1455 / 2720699 PCT/US2012042311
Applicant/Proprietor	
Hale BioPharma Ventures, LLC	

Communication pursuant to Rules 70(2) and 70a(2) EPC

A supplementary European search report has been drawn up concerning the above-identified European patent application (publication number: 2720699).

Since the request for examination has been filed (R. 70(1), 159(1)(f), Art. 94(1) EPC) prior to the transmission of the supplementary European search report, you are hereby invited to indicate within

six months

of notification of this communication whether you wish to proceed further with the European patent application.

If you do not indicate in due time that you wish to proceed further with the European patent application, it **will be deemed to be withdrawn** (R. 70(3) EPC).

You are invited, within the above-mentioned six-month period, to comment on the objections raised in the opinion accompanying the European search report and/or to file any amendments to the description, claims and drawings correcting any deficiencies noted in the opinion (R. 70a(2), R. 137(2) EPC; Guidelines for Examination in the EPO, B-XI, 8).

If filing amendments, you must identify them and indicate the basis for them in the application as filed. Failure to meet either requirement may lead to a communication from the Examining Division requesting that you correct this deficiency (R. 137(4) EPC).

Should the reply to the invitation pursuant to Rule 70a(2) EPC be filed in an admissible non-EPO language, a translation is to be submitted within one month of its filing (R. 6(2) EPC).

Should you not comply with this invitation within the time limit, the application **will be deemed to be withdrawn** in accordance with Rule 70a(3) EPC.

Receiving Section

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EPO Form 1224 11.12 (RTB/ESOP01=N) DMEX

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Date
04.08.15

Reference	Application No./Patent No.
EPA-124 519	12801372.9 - 1455 / 2720699 PCT/US2012042311
Applicant/Proprietor	
Hale BioPharma Ventures, LLC	

Notice drawing attention to Rule 51(2) EPC, Article 2 No. 5 of the Rules relating to Fees,
- Payment of the renewal fee plus additional fee -

The renewal fee for the 04. year fell due on 30.06.15 unless this date falls within the period covered by an interruption of the proceedings in accordance with Rule 142(1) EPC, or a request for re-establishment of rights is pending (Art. 122, R. 51(4) EPC).

The current rate of the renewal fee amounts to **EUR 580,00** (see current Schedule of fees and costs).

The renewal fee was not paid by the due date.
The renewal fee may still be validly paid **up to the last day of the sixth calendar month** following the due date, provided that the additional fee (**50%** of the renewal fee) is paid at the same time, see OJ EPO 2008, 5.

Within the above period, which cannot be extended, the following fees are to be paid:

Renewal fee for the 04. year:	EUR	580,00
Additional fee:	EUR	290,00
TOTAL AMOUNT	EUR	870,00

If the renewal fee and the additional fee are not paid in due time, the European patent application shall be deemed to be withdrawn (Art. 86(1) EPC).

Note to users of the automatic debiting procedure
The normal time limit for payment of the above renewal fee had already expired when the automatic debit order was received. The renewal fee and the surcharge will be debited automatically on the last day of the six-month period (supplementary publication 3 - OJ EPO 2015).

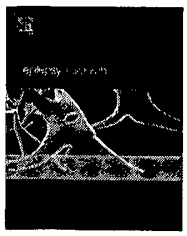
Important information concerning fee amounts
Following any amendment to the Rules relating to Fees, the amount(s) mentioned in this communication may be different from the amount(s) **actually due on the date of payment.** The latest version of the Schedule of fees and expenses, published as a Supplement to the Official Journal of the EPO, is also available on the EPO website (**www.epo.org**) and can be found under **www.epo.org/schedule-of-fees**, which allows the viewing, downloading and searching for individual fee amounts, both current and previous.
Please note that procedural fees are usually adjusted every two years, on even years, with effect from 1 April.

Payments by cheque delivered or sent direct to the EPO are no longer accepted as from 1 April 2008 (see OJ EPO 2007, 626).

Receiving Section

Epilepsy Research (2013) 105, 362–367

journal homepage: www.elsevier.com/locate/epilepsyres



A pilot study assessing the bioavailability and pharmacokinetics of diazepam after intranasal and intravenous administration in healthy volunteers

Suresh K. Agarwal[a,b,*], Robert L. Kriel[a,b], Richard C. Brundage[a,b], Vijay D. Ivaturi[a,b,c], James C. Cloyd[a,b]

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Received 4 September 2012; received in revised form 30 January 2013; accepted 27 February 2013
Available online 2 April 2013

KEYWORDS
Acute repetitive seizures;
Diazepam;
Intranasal therapy;
Seizure emergencies;
Out-of-hospital

Summary Diazepam rectal gel (Diastat®) is the only FDA-approved product indicated for acute repetitive seizures. Despite its proven efficacy, most older children and adults object to this route of administration. As a result, many patients do not realize the benefit of a therapy that can improve outcomes and decrease healthcare costs. Intranasal administration of benzodiazepines offers a potential alternative. The primary objective of this study was to compare the bioavailability and pharmacokinetics of two novel intranasal (IN) diazepam (DZP) formulations versus intravenous (IV) administration in healthy volunteers. Twenty-four healthy volunteers were randomized into an open-label, three-way crossover study. 10 mg doses of two investigational intranasal DZP formulations (solution, suspension) and a 5 mg IV dose of commercially available DZP injectable, USP were given. A two-week washout period separated treatments. Plasma samples for DZP analysis were collected pre-dose and at regular intervals up to 240 h post-dose. DZP concentration–time data were analyzed using a non-compartmental pharmacokinetics approach. Exposure following administration of DZP IN solution (absolute bioavailability – 97%) was greater than the IN suspension (absolute bioavailability – 67%). Mean C_{max} values for the suspension and solution formulations were 221 ng/mL and 272 ng/mL, respectively. Median time to maximum concentration (T_{max}) was 1 h and 1.5 h for suspension and solution formulation, respectively. Both investigational intranasal formulations were well tolerated. The results of this pilot study indicate that development of an intranasal diazepam formulation with high bioavailability, reasonable variability, and good tolerability is feasible.

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E-mail address: agar0152@umn.edu (S.K. Agarwal).

0920-1211/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.eplepsyres.2013.02.018

Introduction

Seizure emergencies are associated with high morbidity and mortality which can be reduced by prompt and appropriate pharmacological therapy. During a seizure, there is an increased release of excitatory neurotransmitters, usually glutamate and/or aspartate. Normally, an increase of the inhibitory neurotransmitter, gamma aminobutyric acid (GABA) will result in cessation of the seizure (Dalby and Mody, 2001). However, if GABA is not released promptly, excess excitation may lead to loss of neural control and convulsive seizures. In 1993, Epilepsy Foundation of America's Working Group on Status Epilepticus recommended that antiepileptic drug administration should be initiated whenever a seizure has lasted 10 min (Working Group on Status Epilepticus, 1993). A recent review article suggested that most epileptic seizures last 1–4 min and seizures lasting greater than 5 min should be treated as status epilepticus (Kälviäinen et al., 2009). Evidence suggests that the longer a seizure continues, the less likely it is to spontaneously stop (Shinnar et al., 2008) and can also progress to status epilepticus, which is associated with increased morbidity and mortality, suggesting a need for prompt therapy (Lowenstein et al., 1999).

The standard treatment for seizure emergencies is intravenous administration of benzodiazepines, usually lorazepam or diazepam followed by phenytion or fosphenytoin (Lowenstein and Alldredge, 1998). Although intravenous route is the most effective option for quick cessation of seizures, therapy gets delayed as it requires skilled medical personnel and transportation to medical facility. Diazepam rectal gel (Diastat®) is the only formulation of diazepam indicated for the out-of-hospital management of selected, refractory patients who require intermittent use of diazepam to control bouts of increased seizure activity such as acute repetitive seizures. Introduction of rectal diazepam products in Europe and in the United States dramatically changed the management of seizure emergencies. With these formulations, caregivers were able to achieve good outcomes by initiation of early treatment after the onset of acute repetitive and prolonged seizures. As a result, emergency department admissions have declined with a decrease in health care costs and improved quality of life (Kriel et al., 1991). Nonetheless, social objections by older children and adults and legal concerns about rectal administration have limited its use. As a result, many patients do not realize the benefit of a therapy that can improve outcomes and decrease healthcare costs. Shortly after the introduction of rectal diazepam, a need for alternative route of administration was realized and interest emerged to investigate and develop different formulations of benzodiazepines (clonazepam, diazepam, lorazepam, and midazolam) using one or more routes of administration such as buccal, intramuscular and nasal.

Intranasal benzodiazepines appear to be particularly promising and several research groups carried out studies to investigate the pharmacokinetics, bioavailability and tolerability (Lau and Slattery, 1989; Burstein et al., 1997; Wermeling et al., 2001, 2006, 2009; Knoester et al., 2002; Dale et al., 2006; Ivaturi et al., 2009; Haschke et al., 2010; Veldhorst-Janssen et al., 2011; Anderson et al., 2012; Hardmeier et al., 2012). To meet the need of an alternate therapy for seizure emergencies, our group has investigated several intranasal formulations of diazepam. Our earlier studies have demonstrated the feasibility of nasal administration of diazepam (Ivaturi et al., 2009). Diazepam was absorbed rapidly following nasal administration and the pharmacokinetic profile of intranasal formulations compared favorably to that of the rectal diazepam gel. However, the tolerability was only moderate. The results of earlier studies concluded that intranasal diazepam offers a viable alternative to rectal administration, however further enhancement of formulations was needed to both improve tolerability and the extent and consistency of absorption. In the current study, two novel formulations of diazepam nasal spray have been evaluated and compared with intravenous administration. The primary objective of this study was to assess the bioavailability and pharmacokinetics (PK) of diazepam after intranasal administration of solution and suspension formulations in healthy volunteers under fasted conditions. The secondary objective of this study was to assess the safety and tolerability of these two diazepam nasal spray formulations after a single administration.

Methods

Subjects and study design

Subjects were healthy volunteers 18–45 years old with BMI between 19 and 30 kg/m^2, who provided informed consent and were compensated for participation. Subjects with known history of severe seasonal or non-seasonal allergies, having nasal polyps or any nasal passage abnormality that could interfere with nasal spray administration were excluded. Subjects who were pregnant or lactating, smoking or using tobacco products within the 6 months prior to the first dose of the study drug, allergic to diazepam, or have been on restrictive diet were also excluded. The study was approved by the Institutional Review Boards at the University of Minnesota and was conducted at PRISM Clinical Research Unit (CRU) in St. Paul, MN. The principal investigator was present at the CRU during and following drug administration.

The study utilized a randomized, open-label, six sequence, three-way crossover design to compare the pharmacokinetics and bioavailability of a commercially available parenteral DZP administered intravenously (5 mg) with two novel intranasal DZP formulations (10 mg). Twenty four subjects received the two intranasal and one intravenous dose of DZP with a two-week washout period between doses. Prior to each of the three treatments, the subject's eligibility was reviewed. Subjects were instructed to abstain from prescription drugs and over the counter medications, 14 days and 7 days prior to the first dose of study, respectively. Treatment with any known enzyme altering drugs such as barbiturates, phenothiazines, cimetidine, carbamazepine, within 30 days prior to the first dose of study drug or during the study was also one of the exclusion criteria. Subjects were admitted to the study unit no later than 1900 h of the evening prior to study drug administration. The next morning, following an overnight fast, subjects were randomized to receive 10 mg intranasal dose of DZP solution, or 10 mg intranasal dose of

DZP suspension, or 5 mg intravenous dose of DZP. Subjects fasted for an additional 4 h after the diazepam dose. Water consumption was restricted from 1 h prior to dosing until 1 h postdose.

Study drugs

The intravenous formulation used in this study was the commercially available parenteral DZP (diazepam injectable, 5 mg/mL, USP). A single 5 mg diazepam injection was given intravenously, over one minute, as directed in the product package insert. The intranasal DZP formulations were supplied by Neurelis, Inc. The intranasal diazepam dose of 10 mg in 0.1 mL was administered using the Pfeiffer/Aptar sprayer which is commercially available, with the subject lying in the semi-recumbent position.

Drug assay

Blood samples (6 mL) for the measurement of plasma concentrations of diazepam were collected in blood collection tubes containing K_2-EDTA at the following times relative to dosing: prior to dosing and at 2.5, 5, 10, 15, 20, 30, and 45 min and at 1, 1.5, 2, 4, 8, 12, 24, 36, 48, 72, 96, 144, 192, and 240 h from the start of the intravenous infusion or after an intranasal dose. Plasma was separated by centrifugation and frozen at approximately −20 °C, pending analysis by LC/MS/MS.

To prepare a sample for analysis, 20 μL of a 10 ng/mL diazepam-d_5 solution (internal standard) and 0.2 mL of water was added to a 50 μL of K_2-EDTA human plasma. The samples were vortexed, extracted using ABN SPE plates, eluted with methanol and taken to dryness under nitrogen at approximately 40 °C. The dried residues were reconstituted in 200 μL of 1:1 methanol:water. After one minute of vortex mixing, 15 μL of the sample solution was injected onto the LC/MS/MS system. Standard curves over a range of 0.1–100 ng/mL and quality control DZP samples containing 0.3 (low), 6 (medium) and 80 ng/mL (high) were prepared.

Pharmacokinetic analysis

DZP concentration–time data were analyzed using a non-compartmental pharmacokinetic approach with Phoenix software (version 6.2; Pharsight Corporation, Mountain View, CA, USA). The terminal rate constant (λz) was determined from the slope of the terminal log-linear portion of the plasma concentration–time curve, and the terminal half-life ($T_{1/2}$) was calculated as $\ln 2/(\lambda z)$. Maximum plasma concentrations (C_{max}) and time to maximum concentration (T_{max}) were determined by direct observation of the data. The area under the concentration–time (AUC) curve to the last non-zero plasma concentration (C_{last}) that was above the lower limit of quantification (0.1 ng/mL) was calculated as AUC_{last}. The area under the concentration–time curve extrapolated to infinity ($AUC_{0-\infty}$) was calculated as $AUC_{last} + (C_{last}/\lambda z)$. Means and standard deviations for the parameters were also obtained using the descriptive statistics tool in Phoenix version 6.2.

Safety evaluation

Safety was assessed by adverse event monitoring, clinical laboratory evaluations, changes in vital signs measurements, physical examinations, and ECG results. Nasal irritation was evaluated by a trained observer within two (2) hours before and post-dose following the one-hour PK sample and the 24-hour PK sample using the following nasal irritation scale:

0 – Normal appearing mucosa, no bleeding.
1 – Inflamed mucosa, no bleeding.
2 – Minor bleeding which stops within 1 min.
3 – Minor bleeding, taking 1–5 min to stop.
4 – Substantial bleeding for 4–60 min, does not require medical intervention.
5 – Ulcerated lesions, bleeding which requires medical intervention.

A sedation scale was used to assess the degree of drowsiness of the subjects after administration of the intranasal and intravenous diazepam formulations. Sedation scores were reported by the subject (if awake) as well as by a trained observer using the same rating scale, just prior to (baseline) and at 5, 15, 30, 60 min and at 2,3,4,6 and 8 h post dose. The sedation scale used for rating drowsiness consisted of the following options:

- 0 – Alert, not drowsy; normal conversation.
- 1 – Awake, talking; but somewhat drowsy.
- 2 – Napping or sleeping, but easily awakened.
- 3 – Sleeping, awakened only with loud voice or shaking.
- 4 – Sleeping, very difficult to awaken; promptly returns to sleep.
- 5 – Sleeping, cannot awaken.

Statistical analysis

Statistical analysis of PK parameters C_{max}, AUC_{last} and $AUC_{0-\infty}$ was done after log transformation. Repeated measures ANOVA followed by Tukey's multiple comparison test was used to test for statistical differences in AUC and $T_{1/2}$ among the intranasal and IV formulations. A paired t test was employed to determine if statistical differences existed in C_{max}, the maximum observed concentration, between the two intranasal formulations. A Wilcoxon matched-pairs, signed-ranks test was used to test for a statistical difference in T_{max}, the time to maximum plasma concentration, between the two intranasal formulations.

Results

All 24 subjects (19 male and 5 female) completed the study. The mean (±SD) weight of the 24 subjects was 78.1 (±11.0) kg. The age range of subjects was 21–45 years, with a mean of 32.6 years.

A summary of the pharmacokinetic parameters is presented in the Table 1. It is to be noted that there were 4 subjects each for the suspension and solution treatments for whom a valid estimate of λz could not be calculated and thus $AUC_{0-\infty}$ and $T_{1/2}$ were not calculated either. This was either due to lack of a log-linear decay, a coefficient

Table 1 Mean ± SD of DZP pharmacokinetic parameters following intranasal (10 mg) and intravenous (5 mg) administration in 24 healthy volunteers.

Pharmacokinetic parameter [a]	10 mg Nasal suspension Mean ± SD	10 mg Nasal solution Mean ± SD	5 mg intravenous Mean ± SD
C_{max} (ng/mL)	221 ± 78.6[d]	272 ± 100	–
T_{max} (hr) [b]	1.00 [0.6–2.0]	1.50 [0.8–4.0]	–
AUC_{last} (ng h/mL)	5229 ± 1463[e]	7340 ± 1882	3832 ± 1150
$AUC_{0-\infty}$ [c] (ng h/mL)	5381 ± 1409[e]	7338 ± 2072	4104 ± 1318
Bioavailability	67%	97%	–
$T_{1/2}$ (hr) [c]	56.2 ± 23.0	49.2 ± 16.9	56.2 ± 21.0

[a] Mean values are presented as arithmetic means.
[b] Median (min, max) reported for T_{max}.
[c] $N = 20$ for nasal suspension and nasal solution. There were 4 subjects each for the suspension and solution treatments for whom a valid estimate of λz could not be calculated and thus $AUC_{0-\infty}$ and $T_{1/2}$ were not calculated either. This was either due to lack of a log-linear decay, a coefficient of determination (r^2) < 0.9000, or an extrapolated AUC that was >20% of $AUC_{0-\infty}$.
[d] Two-tailed p value <0.05 (paired t-test).
[e] Nasal suspension vs. IV and nasal solution – p value <0.05 (Tukey's multiple comparison test).

of determination (r^2) < 0.9000, or an extrapolated AUC that was >20% of $AUC_{0-\infty}$. The mean concentration time profiles for all the three arms are shown in the Fig. 1. DZP concentrations rose rapidly and were maintained for several hours following administration of both intranasal formulations. The mean intranasal DZP suspension C_{max} and T_{max} were 221 ± 78.6 ng/mL and 1.25 ± 0.5 h respectively. The mean intranasal DZP solution C_{max} and T_{max} were 272 ± 100 ng/mL and 1.51 ± 0.88 h respectively. Median T_{max} values for the suspension and solution formulations were similar to the mean values: 1 h and 1.5 h, respectively. Total systemic exposure following administration of DZP intranasal solution (absolute bioavailability – 97%) was greater than that of the intranasal suspension (absolute bioavailability – 67%). The mean elimination $T_{1/2}$ was comparable for all three formulations indicating that there was no prolonged absorption of diazepam following intranasal administration (Fig. 2).

Both investigational intranasal formulations were well tolerated. Overall, 71% of subjects experienced ≥1 treatment-emergent adverse effects (AEs) during the study, with similar numbers of subjects experiencing AEs after administration of intranasal suspension (9 subjects), intranasal solution (8 subjects), and IV diazepam (10 subjects). The most commonly reported AEs were epistaxis and somnolence (6 subjects each). Mild, self-limited epistaxis (a few drops of blood in either nostril) was observed following administration of IV diazepam (3 subjects, 5 events), intranasal solution (3 subjects, 3 events) and intranasal suspension (1 subject, 1 event). Somnolence was more frequently associated with IV diazepam (4 subjects) than with either of the intranasal diazepam formulations (1 subject each). All treatment-emergent AEs were characterized by the investigator as being mild or moderate in severity. There were no AE reports of nasal pain by any subject in any treatment period. Thirteen subjects experienced AEs that were considered by the investigator to be related to intranasal study drug formulations. Most common AEs were headache, somnolence, epistaxis, and nasal discomfort. No AE met the

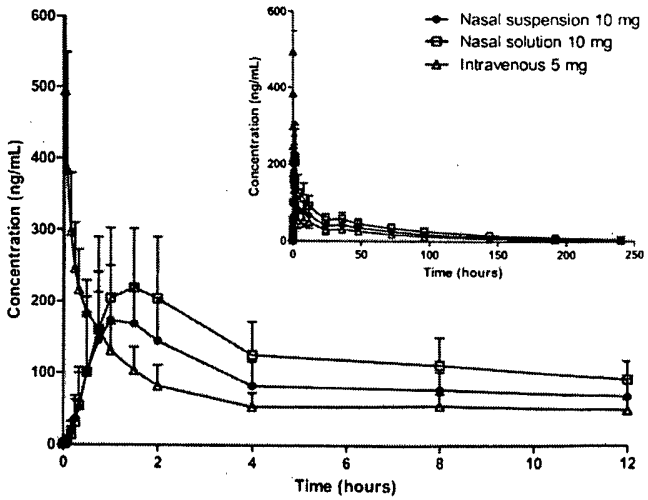

Figure 1 Mean (+standard deviation) plasma concentration–time profiles of diazepam after intravenous and intranasal administration in twenty-four subjects (0–12 h). Inset shows the complete profile (0–240 h).

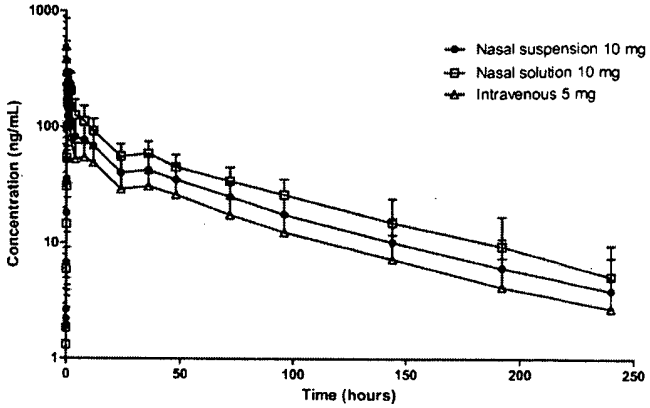

Figure 2 Mean (+standard deviation) plasma concentration–time profiles of diazepam after intravenous and intranasal administration in twenty-four subjects (semi-logarithmic scale).

criteria of a serious adverse event, and none resulted in a subject's withdrawal from the study.

Discussion

The absolute bioavailability of intranasal solution approached 100% and was higher than that reported in prior intranasal diazepam studies, while variability in exposure (AUC) for both the suspension and the solution was similar to the IV dose (Table 1). Our results compare favorably with studies involving rectal administration of diazepam. Milligan et al. administered a 20 mg rectal DZP solution to 10 epilepsy patients. The onset of reduction in EEG spike counts occurred approximately 15–20 min after drug administration and was associated with a plasma DZP concentration of approximately 200 ng/mL. The 60% reduction in spike counts and DZP concentrations above 200 ng/ml were sustained for the duration of the 3 h observation period (Milligan et al., 1982). In our current study, for both the formulations, the mean C_{max} following a 10 mg dose was above the 200 ng/mL threshold associated with a reduction in spike counts. Following intranasal solution administration, 18 out of 24 subjects attained DZP concentrations above the 200 ng/mL threshold. By comparison, following the intranasal suspension administration 15 out of 24 subjects attained DZP concentrations greater than 200 ng/mL threshold.

The intranasal solution formulation had an absorption and elimination profile similar to that observed for the commercially available DZP rectal gel (Diastat®) as reported by our group. The absolute bioavailability of the nasal solution was approximately 10% greater than that reported for DZP rectal gel (Diastat®), but half-life, T_{max} and dose-adjusted C_{max} were comparable (Cloyd et al., 1998). In that bioavailability study, we found a mean C_{max} of 447 ± 91.1 ng/ml following 15 mg dose of diazepam rectal gel administration. In the present study, the average C_{max} for the 10 mg dose of the intranasal solution formulation was approximately 270 ng/mL. Ivaturi et al. reported a linear increase in C_{max} with diazepam dose reflecting approximate dose proportionality (Ivaturi et al., 2009). Assuming a linear increase in C_{max} occurs with the intranasal solution of diazepam formulation used in the current study, increasing the dose to 15 mg from 10 mg should result in peak concentrations in the range of 400 ng/mL. The mean concentrations for the intranasal solution were maintained above100 ng/mL until approximately 8 h after the drug administration. Assuming linear pharmacokinetics, doubling the dose from 10 mg to 20 mg will result in concentrations above 200 ng/mL for about 8 h.

A critical factor when considering intranasal benzodiazepine therapy for seizure emergencies is the time to reach a targeted drug concentration. As compared to the rectal study using the commercially available diazepam rectal gel, the intranasal formulations in the present study exhibited a comparable rate of absorption. In our rectal gel study, we reported an initial peak concentration of 375 ng/mL at 45 min and a second peak of 447 ng/mL at 70 min. The intranasal suspension and solutions used in the current study attained average peak concentrations at 60 min and 90 min respectively.

One of our key findings was that the variability in exposure (AUC) for both the solution and suspension was similar to IV dose (coefficient of variation, 30%). The rectal gel study reported an absolute bioavailability of approximately 90%. Simulations are needed to determine the sample size required to show bioequivalence between the rectal gel and the intranasal solution. Our study was intended to serve as a pilot study to provide information on the suitability of one or both formulations for further development. The information gained from this study can be used to design future, adequately powered bioavailability and bioequivalence studies.

Prior studies with diazepam and midazolam reported dual peaks reflecting oral absorption in which the first peak representing nasal absorption occurs within 20–30 min and a second peak presumably due to enteral absorption occurs around 1–2 h after intranasal drug administration. In some of the studies reporting dual peaks, subjects actually commented that they swallowed a portion of dose administered intranasally (Ivaturi et al., 2009). Second diazepam peak concentrations were not observed in our current study results.

Our earlier studies with a glycofurol based intranasal formulation of diazepam resulted in 75% and 74% bioavailability after administration of 5 and 10 mg DZP doses, respectively (Ivaturi et al., 2009). The formulations were

absorbed rapidly but the tolerability was poor which made it unsuitable for further development. Subsequently, two other intranasal formulations compared the pharmacokinetics and tolerability with rectal diazepam gel. In that study, the pharmacokinetic profiles of the two investigational diazepam formulations were comparable to that of rectal diazepam gel. No serious adverse effects were reported following administration of intranasal formulations; however, majority of the subjects reported nasal discomfort or pain immediately after dose administration. In this current study, both diazepam nasal spray formulations were remarkably well-tolerated. There were no AE reports of nasal pain by any subject in any treatment period. It is noteworthy that intranasal administration of diazepam did not appear to cause epistaxis – more epistaxis events were reported following IV diazepam than after administration of either intranasal formulation. Nasal drug delivery can cause epistaxis and other nasal diazepam formulations may carry this risk, but the most plausible explanation for epistaxis in our study following IV administration is that individuals occasionally experience minor nose bleeds in harsh winters with dry interior environment. The nasal DZP solution shows promise as a socially acceptable, well-tolerated, easily administered formulation for use in seizure emergencies. Its pharmacokinetic profile is similar to rectally administered diazepam with high bioavailability, reasonable variability, and rapid attainment and maintenance of therapeutic drug concentrations. The absolute bioavailability of the intranasal solution was approximately 100% and was higher than that reported in prior intranasal diazepam studies. Variability in exposure (AUC) for both the suspension and solution was similar to the IV dose. The results of this pilot study indicate that development of an intranasal diazepam formulation with high bioavailability, reasonable variability, and good tolerability is feasible.

Acknowledgements

We would like to acknowledge Neurelis Inc., for providing the study drug and also for their financial support towards this study. We would like to acknowledge William Kramer, Kramer Consulting LLC for assistance with analysis of the data. Plasma diazepam concentrations were determined by LC/MS/MS at ICON Development Solutions LLC.

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European Patent Application 12 801 372.9-1455 based on PCT/US2012/042311
Title: Administration of benzodiazepine
Applicant: Hale BioPharma Ventures, LLC
Our ref.: EPA-124 519

In response to the Communication under Rules 70(2) and 70a(2) EPC dated 13 April 2015:

I Requests

1 Applicant wishes to proceed further with the present application.

2 It is requested to grant a European patent based on:

- the revised set of claims 1-15 submitted herewith (replacing previous claims 1-15 as on file); and

- original description pages 1-65 and drawing sheets 1/5-5/5. It is requested to defer any adaption of the description until the claims are considered allowable.

3 Should the application not be considered allowable, it is requested to issue a Communication according to Article 94(3) EPC. In particular, in light of decision **G 1/10** and the procedure under current Rules 71(3) and (6) EPC, it is respectfully requested that the Examining Division refrains from effecting any amendments when issuing a Communication under Rule 71(3) EPC without the prior consent of the Applicant.

4 Purely as a matter of precaution, we request that oral proceedings under Article 116 EPC be held only in the event that the Examining Division intends to refuse the application. However, if the hearing should take place either in The Hague or in Berlin, it is respectfully requested that a date for the oral proceedings be set allowing that same can be held by video-conference. In this case, the representative intends to use IP technology.

II Amendments

Claim 1 has been reworded into a *second medical use* claim, i.e. use of the nasal pharmaceutical solution for the treatment of seizures. Basis for the treatment of seizures can e.g. be found at paragraph [083] of the original application, see also former claim 15. The remaining claims have been adapted accordingly. Furthermore, claims 14 and 15 have been amended to specify the components of the pharmaceutical solution. A complete basis for the claims may be found at, but is not limited to:

Claim No.	Basis in PCT/US2012/042311 as filed
1	[010], [011], [072], [083], [084], original claims 1, 8,
2	[010], [011], [022], [079], [085]-[0133], [0173], original claim 3
3	[010], [011], [022], [035]-[039], [043], [057], [079], [091]-[096], [0112], [0118], [0154], [0155]
4	[010], [011], original claim 5, 28
5	[010], [011], original claim 6, 29
6	[010], [011], [014], [023], [044], [058], [0138], Original claim 7, 30
7	[010], [011], original claim 10, 33
8	[010], original claim 11
9	[017], [026], [047], [061], original claim 13, 36
10	[010], [011], original claim 17, 56, 57, 60
11	[010], original claim 18, 19, 49, 50
12	[010], [011], original claim 19, 22, 51, 54, 56, 57-62
13	Original claim 21, 22, 57, 58,
14	[010], [011], original claim 22, 54, 56, 57, 60
15	Original claim 22, 54

III Clarity (Article 84 EPC)

Applicant has removed the term "about" from claims 1, 4, 5, 9, 11, and 12.

Applicant has removed the term "derivatives" from claim 6. Applicant also notes that claim 13 has been amended such that the objection to "consisting essentially of" is now moot.

In view of the above claim amendments, the objections under lack of clarity are rendered moot. The present claims fulfill the requirements of Article 84 EPC in full.

IV Novelty (Article 54 EPC)

Applicant has amended claims 1-15, such that they recite a *second medical use*.

None of the cited documents discloses a pharmaceutical solution having a composition as defined in claim 1 for nasal administration for treating seizures.

Although D6 mentions the treatment of seizures, it also mentions other diseases such as e.g. insomnia, anxiety, muscle spasms, rigidity and the symptoms of drug withdrawal (see [0077] of D6).

Furthermore, although D6 mentions the possibility of using ethanol and benzyl alcohol within a group of possible alcohols or combinations of alcohols (see e.g. [0023] of D6), there is no pointer to the claimed specific combination of alcohols.

Therefore, the claimed specific combination of features is neither directly nor unambiguously disclosed in D6.

Applicant, hence, believes that the proposed amendments render the objections under Art 54 EPC moot.

V Inventive Step (Article 56 EPC)

The Search Opinion asserts a lack of inventive step between claims 1-15 of the present application, and reference D6. Applicant contends that the combination of ethanol and benzyl alcohol in the amounts claimed provides unexpected benefits in the context of treating seizures, such that a person of skill in the art would be surprised in light of the prior art.

The present application contains Figures 1-3, which compare traditional intravenous (IV) administration of diazepam, with a diazepam nasal suspension (containing diazepam, Vitamin E, and propylene glycol), and the diazepam nasal solution of the present application (containing diazepam, Vitamin E, ethanol, and benzyl alcohol). The nasal solution of the present application yields the highest diazepam plasma concentration of the three treatments. Further, Table 11-3 indicates that diazepam nasal solution administration produces the greatest area under the curve (AUC), of the three treatments. Therefore, the data indicate the diazepam nasal solution of the present application gives a patient the greatest total drug exposure over time for the three treatments tested.

We herewith file an article published by Agarwal *et al.*, as post-published evidence, which is the publication of the pharmacokinetic (PK) study exemplified in the instant application. Agarwal *et al.*, "A pilot study assessing the bioavailability and pharmacokinetics of diazepam after intranasal and intravenous administration in healthy volunteers," Epilepsy Research (2013), vol. 105, pp. 362-367. As Agarwal *et al.* explain, while intranasal diazepam had been shown to be promising, "further enhancement of the formulations was needed to both improve tolerability and the extent and consistency of absorption. Agarwal *et al.* at p. 363, column 2. As Agarwal *et al.* found, the intranasal solution, which is a benzyl alcohol, ethanol solution falling within the current set of claims, demonstrated a high degree of bioavailability (approximately 100%), which was higher than that reported in prior intranasal diazepam studies. Agarwal *et al.* at p. 367, column 1.

Further, it is known that intranasal administration of alcohols can irritate mucus membranes. However, the diazepam solution of the present application was found to be well-tolerated with only mild adverse events reported. *See*, for example, Specification paragraph [0236].

Agarwal *et al.* stated, for example, that administration of intranasal diazepam did not appear to cause epistaxis (nose bleed), despite poor tolerability of previous intranasal formulation. Agarwal *et al.* at p. 367, column 1.

Therefore, the objective underlying the claims of the present application can be formulated as providing an improved treatment of seizures.

This improvement is provided by the claimed nasal pharmaceutical solution including a combination of ethanol and benzyl alcohol.

None of the cited prior art documents teaches that an improved treatment of seizures can be achieved when using a combination of ethanol and benzyl alcohol in a nasal pharmaceutical solution comprising a benzodiazepine drug.

Therefore, Applicant submits that combining ethanol and benzyl alcohol to produce an intranasal product that provides superior drug exposure yet is non-irritating was not obviously deducible based on the available prior art.

In view of the above facts and arguments, Applicant submits that the requirement of Article 56 EPC is met by the claimed subject-matter.

VI Summary and Final Remarks

In summary, Applicant submits that the claimed subject-matter meets the patentability requirements of the EPC. Should there remain any issues that can be resolved by an informal call, the Examiner is kindly invited to contact the undersigned over the telephone. Also, the Examining Division is respectfully requested to telephone the undersigned or to issue a further Examination Report if the Examining Division is minded to issue a Communication under Rule 71(3) EPC but wishes to propose amendments to the claims or the specification.

Dr. Hendrik Wichmann
European Patent Attorney

Enclosures:
Amended set of claims 1-15 (marked-up version and clean copy)
Article of Agarwal et al., Epilepsy Research **2013**, *105*, 362-367.

CLAIMS

1. A pharmaceutical solution for nasal administration consisting of:

(a) a benzodiazepine drug;

(b) one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from ~~about~~ 30% to ~~about~~ 95% (w/w);

(c) ethanol and benzyl alcohol, in a combined amount from ~~about~~ 10% to ~~about~~ 70% (w/w); and

(d) an alkyl glycoside,

for use in a method of treating seizures.~~,~~

2. The pharmaceutical solution for use according to~~of~~ claim 1, wherein the benzodiazepine drug is selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, any pharmaceutically-acceptable salts thereof, and any combinations thereof.

3. The pharmaceutical solution for use according to~~of~~ claim 2, wherein the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof.

4. The pharmaceutical solution for use according to~~of~~ claim 1, containing ~~about~~ 1 to ~~about~~ 20% (w/v) of benzodiazepine.

5. The pharmaceutical solution for use according to~~of~~ claim ~~5~~4, containing ~~about~~ 1 to ~~about~~ 20% (w/v) of diazepam.

6. The pharmaceutical solution for use according to~~of~~ claim 1, wherein the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β- tocotrienol, γ- tocotrienol, δ-tocotrienol, tocophersolan, any isomers thereof, any esters thereof, any analogs ~~or derivatives~~ thereof, and any combinations thereof.

7. The pharmaceutical solution for use according to ~~of~~ claim 1, containing 1-25% (w/v) ethanol and 1-25 % (w/v) benzyl alcohol.

(markup)

8. The pharmaceutical solution for use according to~~of~~ claim 1, containing 10-22.5% (w/v) ethanol and 7.5-12.5% (w/v) benzyl alcohol.

9. The pharmaceutical solution for use according to~~of~~ claim 1, wherein the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from ~~about~~ 45% to ~~about~~ 85% (w/w).

10. The pharmaceutical solution for use according to~~of~~ claim 1, consisting of 5-15% (w/v) diazepam, 0.01-1% (w/v) alkyl glycoside, 45-65% (w/v) vitamin E, 10-25% (w/v) ethanol and 5-15% (w/v) benzyl alcohol.

11. The pharmaceutical solution for use according to~~of~~ claim 1, wherein the pharmaceutically-acceptable formulation comprises at least ~~about~~ 0.01% (w/w) of an alkyl glycoside.

12. The pharmaceutical solution for use according to~~of~~ claim 11, wherein the pharmaceutically-acceptable formulation comprises ~~about~~ 0.01% to 1% (w/w) of dodecyl maltoside.

13. The pharmaceutical solution for use according to~~of~~ claim 1, consisting ~~essentially~~ of diazepam, vitamin E, ethanol, benzyl alcohol, and dodecyl maltoside.

14. The pharmaceutical solution for use according to~~of~~ ~~one of~~ claims 1 ~~-13~~, consisting of 5-15% (w/v) diazepam, 45-65% (w/v) vitamin E, 10-25% (w/v) ethanol, 5-15% (w/v) benzyl alcohol, and 0.01%-1% (w/v) dodecyl maltoside. ~~for intranasal administration for treatment of a patient with a disorder which may be treatable with a benzodiazepine drug.~~

15. The pharmaceutical solution for use according to~~of~~ claim 1 4, consisting of 10% (w/v) diazepam, 56.47% (w/v) vitamin E, q.s. dehydrated ethanol, 10.5% (w/v) benzyl alcohol, and 0.25% (w/v) dodecyl maltoside~~wherein the disorder is seizure.~~.

(markup)

CLAIMS

1. A pharmaceutical solution for nasal administration consisting of:

(a) a benzodiazepine drug;

(b) one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from 30% to 95% (w/w);

(c) ethanol and benzyl alcohol, in a combined amount from 10% to 70% (w/w); and

(d) an alkyl glycoside,

for use in a method of treating seizures.

2. The pharmaceutical solution for use according to claim 1, wherein the benzodiazepine drug is selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, any pharmaceutically-acceptable salts thereof, and any combinations thereof.

3. The pharmaceutical solution for use according to claim 2, wherein the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof.

4. The pharmaceutical solution for use according to claim 1, containing 1 to 20% (w/v) of benzodiazepine.

5. The pharmaceutical solution for use according to claim 4, containing 1 to 20% (w/v) of diazepam.

6. The pharmaceutical solution for use according to claim 1, wherein the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β- tocotrienol, γ- tocotrienol, δ- tocotrienol, tocophersolan, any isomers thereof, any esters thereof, any analogs thereof, and any combinations thereof.

7. The pharmaceutical solution for use according to claim 1, containing 1-25% (w/v) ethanol and 1-25 % (w/v) benzyl alcohol.

8. The pharmaceutical solution for use according to claim 1, containing 10-22.5% (w/v) ethanol and 7.5-12.5% (w/v) benzyl alcohol.

9. The pharmaceutical solution for use according to claim 1, wherein the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from 45% to 85% (w/w).

10. The pharmaceutical solution for use according to claim 1, consisting of 5-15% (w/v) diazepam, 0.01-1% (w/v) alkyl glycoside, 45-65% (w/v) vitamin E, 10-25% (w/v) ethanol and 5-15% (w/v) benzyl alcohol.

11. The pharmaceutical solution for use according to claim 1, wherein the pharmaceutically-acceptable formulation comprises at least 0.01% (w/w) of an alkyl glycoside.

12. The pharmaceutical solution for use according to claim 11, wherein the pharmaceutically-acceptable formulation comprises 0.01% to 1% (w/w) of dodecyl maltoside.

13. The pharmaceutical solution for use according to claim 1, consisting of diazepam, vitamin E, ethanol, benzyl alcohol, and dodecyl maltoside.

14. The pharmaceutical solution for use according to claim 1, consisting of 5-15% (w/v) diazepam, 45-65% (w/v) vitamin E, 10-25% (w/v) ethanol, 5-15% (w/v) benzyl alcohol, and 0.01%-1% (w/v) dodecyl maltoside.

15. The pharmaceutical solution for use according to claim 1, consisting of 10% (w/v) diazepam, 56.47% (w/v) vitamin E, q.s. dehydrated ethanol, 10.5% (w/v) benzyl alcohol, and 0.25% (w/v) dodecyl maltoside.

Europäisches Patentamt
European Patent Office
Office européen des brevets

Application No.: 12801372.9

Substantive examination has started on 29.06.16 (see Notice from the European Patent Office dated 29.01.2013, OJ EPO 2013, 153).

For the Examining Division

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Application No.	Ref.	Date
12 801 372.9 - 1455	EPA-124 519	05.07.2016
Applicant: Hale BioPharma Ventures, LLC		

Communication pursuant to Article 94(3) EPC

The examination of the above-identified application has revealed that it does not meet the requirements of the European Patent Convention for the reasons enclosed herewith. If the deficiencies indicated are not rectified the application may be refused pursuant to Article 97(2) EPC.

You are invited to file your observations and insofar as the deficiencies are such as to be rectifiable, to correct the indicated deficiencies within a period

of 4 months

from the notification of this communication, this period being computed in accordance with Rules 126(2) and 131(2) and (4) EPC. One set of amendments to the description, claims and drawings is to be filed within the said period on separate sheets (R. 50(1) EPC).

If filing amendments, you must identify them and indicate the basis for them in the application as filed. Failure to meet either requirement may lead to a communication from the Examining Division requesting that you correct this deficiency (R. 137(4) EPC).

Failure to comply with this invitation in due time will result in the application being deemed to be withdrawn (Art. 94(4) EPC).

Registered letter

Gómez Gallardo, S
Primary Examiner
For the Examining Division

Enclosure(s): 5 page/s reasons (Form 2906)

The examination is being carried out on the **following application documents**

Description, Pages

1-65 as published

Claims, Numbers

1-15 received on 21-10-2015 with letter of 21-10-2015

Drawings, Sheets

1/5-5/5 as published

1. CITED DOCUMENT

Reference is made to the following document; the numbering will be adhered to in the rest of the procedure.

D6 US 2009/258865 A1 (HALE BIOPHARMA VENTURES LLC [US]) 15 October 2009 (2009-10-15); cited in the International Search Report

2. AMENDMENTS (Art. 123(2) EPC)

The amendments filed with letter of 21-10-2015 do not contravene the requirements of Art. 123(2) EPC.

3. Art. 54(5) EPC

Claim 1 has been re-worded as a second medical use claim according to Art. 54(5) EPC. It is understood from the letter of 21-10-2015 that the intention of the applicant is that the nasal administration is a limiting feature of the claim. So that this is the case, the claim should, however, be re-drafted to read "A pharmaceutical solution for use in a method of treating seizures wherein the solution is to be administered nasally, the solution consisting of....". In the way the claim is presently drafted, the solution is merely construed as "suitable for nasal administration", without the route of administration being a limiting feature.

4. NOVELTY (Art. 54 EPC)

4.1. The examiner has carefully considered the arguments of the applicant with respect to the novelty of claim 1 but is nevertheless of the opinion that document D6 (originating from the same applicant) still discloses all of the features of this claim.

In this regard, document D6 discloses (cf. paragraphs 34 and 36) an intranasal solution consisting of (a) a benzodiazepine drug (preferably diazepam), (b) one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount of 30-95% (w/w), and (c) one or more alcohols or glycols, or any combinations thereof, in an amount of 10-70% (w/w). In some embodiments, the solution comprises one or more alkyl glycosides (cf. paragraphs 45-47). The one or more alcohols are selected from the group consisting of ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, or any combinations thereof (cf. paragraph 39). The applicant argues with letter of 21.10.2015 that the specific combination of ethanol and benzyl alcohol is neither directly nor unambiguously disclosed in D6, and that there is no pointer to the selection of these two specific alcohols. The examiner does not agree because the mixture of ethanol and benzyl alcohol is one of the possible combinations disclosed in paragraph 39. Any subject-matter that can be derived by one selection from a single list is considered to be directly and unambiguously disclosed. As a matter of fact, having allowed the introduction of a mixture of ethanol and benzyl alcohol in the solution of claim 1 of the present application is based on the same principle of having isolated this combination from a list of different possible solvents or combinations of solvents (cf. paragraph 10 or claim 8 as filed of the present application). In the description of the present application, the combination of ethanol and benzyl alcohol is only explicitly disclosed when linked to the respective amounts of each solvent (i.e. ethanol (1-25% (w/v)) and benzyl alcohol (1-25% (w/v)), or ethanol (10-22.5% (w/v)) and benzyl alcohol (7.5-12.5% (w/v))). The examiner did not object to the generalization of these amounts in claim 1 because the combination of ethanol and benzyl alcohol has been considered to be directly and unambiguously disclosed in view of the list of paragraph 10 or original claim 8 of the present application. Following the same principle, D6 also directly and unambiguously discloses the combination of the two solvents.

The solution of D6 is disclosed as to be used for the treatment of seizures. Once again, the applicant has argued that D6, in particular paragraph 77, only mentions seizures in a list comprising other possible diseases. However, it is clear from paragraphs 78, 82-84, 88-90, 94-96, 100-102, 106-108, 112-114, 119-121, 125-127 and 131, and examples 1, 2, 9 and 10, that the main focus of D6 is on the treatment of seizures, and, therefore, this disease is not just one of many equivalent alternative diseases to be treated. Also in the present application, other diseases are listed in

paragraph 83. However, since the main focus of the application is the treatment of seizures, as evidenced by paragraphs 11, 84, 88-90, 94-96, 100-102, 106-108, 112-114, 118-120, 125-127, 131-133 and 137, and examples 1, 2, and 9-11, this feature has not been considered to result from a selection when assessing whether the requirements of Art. 123(2) EPC are met for claim 1.

If the reasoning of the applicant with letter of 21.10.2015 would be applied for the assessment of added subject-matter in claim 1, this claim would then result from two selections, one for the combination of solvents and one for the treatment of seizures. The examiner has not reasoned in this way. This is why the requirements of Art. 123 (2) EPC are fulfilled for claim 1. The same way of reasoning has to be applied when assessing the novelty of claim 1 in view of D6.

4.2. The examiner is, thus, of the opinion that D6 is detrimental to the novelty of claims 1-6, 9 and 11. Novelty could be easily restored by, for instance, introducing the features of claim 7 in present claim 1 (Art. 54 EPC).

5. INVENTIVE STEP (Art. 56 EPC)

5.1. Document D6 is regarded as the closest prior art. The subject-matter of claim 7 differs from D6 in that the solution contains 1-25% (w/v) of ethanol and 1-25% (w/v) of benzyl alcohol.

To explain the effect of the combination of ethanol and benzyl alcohol, the applicant referred in his letter of 21.10.2015 to the bioavailability study of Table 11-3 performed with (a) the solution of the application comprising diazepam, alpha-tocopherol, ethanol, benzyl alcohol and dodecyl maltoside (Table 11-1), and (b) a suspension of the prior art, said suspension comprising diazepam, vitamin E TPGS, propylene glycol, povidone, methyl paraben, propyl paraben, dodecyl maltoside and water (Table 11-2). According to this study, the solution of the application yields a greater total drug exposure over time compared to the prior art suspension. A post-published article, namely *Agarwal et al, Epilepsy Research (2013), 105, 362-367*, was filed in support of the above, also to justify that the nasal solution of the application is well tolerated without serious adverse effects.

The attention of the applicant is, however, drawn to the fact that the above-mentioned suspension not only differs from the solution in the solvent that has been used but also in the incorporation in the formulation of povidone, methyl paraben, and propyl

paraben. This means that the above prior art suspension is not suitable for comparison purposes, as in said suspension more than one variable has been changed, and, therefore, it is unclear whether the poorer bioavailability is due to the formulation being a suspension instead of a solution, to the suspension containing povidone, or to the suspension containing the two parabens. On the other hand, the nasal suspension of the prior art is also well tolerated, the same as the nasal solution of the application.

Since the data provided so far cannot be considered to be conclusive, the objective technical problem underlying claim 7 has to be regarded as the provision of an alternative nasal solution for treating seizures, the solution consisting of a benzodiazepine drug, 30-95% (w/w) of one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, 10-70% (w/w) of a mixture of ethanol and benzyl alcohol, and an alkyl glycoside.

In the absence of any evidence of an unexpected effect associated therewith, the person skilled in the art would consider adjusting the amounts of ethanol and benzyl alcohol by mere routine experimentation and, by doing so, would inevitably arrive at the amounts of claim 7, without exercising any inventive skill. No inventive step can, therefore, be acknowledged for this claim (Art. 56 EPC). For exactly the same reason, no inventive step can be acknowledged for claim 8 (Art. 56 EPC). The further features of dependent claims 10 and 12-15 are either disclosed in D6 or represent obvious modifications for the skilled person. Therefore, these claims are not inventive either (Art. 56 EPC).

5.2. An inventive step could be acknowledged for claim 7 if it would be demonstrated that an unexpected technical effect is associated with the use of the claimed amounts of ethanol and benzyl alcohol. This effect should be demonstrated by comparison with another nasal solution including exactly the same components but different amounts of the same solvents (Art. 56 EPC).

6. CONCLUSIONS

6.1. Although it was the first intention of the examining division to already summon to oral proceedings, finally, as a favour to the applicant, it was decided to give him a further opportunity to address the objections and amend the claims accordingly, before summons to oral proceedings are drafted. It is hoped that the applicant will use this opportunity to advance the application in an efficient manner. Otherwise, an invitation to oral proceedings is to be expected as the next action from the division.

6.2. When prosecuting the application, the following should be observed:

-An inventive step may be recognized only if the applicant demonstrates that a surprising and/or synergistic effect is attributed to the distinguishing technical feature that the skilled man in the art would not be able to deduct from the prior art. In the absence of a surprising effect directly attributed to the distinguishing feature or evidence of a particular prejudice, an inventive step cannot be acknowledged because the introduced/distinguishing technical feature will be considered as an obvious or arbitrary alternative that the skilled man in the art would perform by routine (Art. 56 EPC).

It should be noted that any argument given with respect to inventive step can only be considered if reflected in the wording of the independent claim(s) by technical features.

6.3. In order to facilitate the examination of the conformity of the amended application with the requirements of Art. 123(2) EPC, the applicant is requested to clearly identify the amendments carried out, irrespective of whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based.

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Europäisches Patentamt

80298 München

14 November 2016

European Patent Application 12 801 372.9-1455 based on PCT/US2012/042311
Title: Administration of benzodiazepine
Applicant: Hale BioPharma Ventures, LLC
Our ref.: EPA-124 519

Further to the Official Communication dated 5 July 2016 it is respectfully requested that the term for responding to the Official Communication be extended by

two months.

Dr. Hendrik Wichmann
European Patent Attorney

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Questions about this communication ?
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Reference	Application No./Patent No.
EPA-124 519	12801372.9 - 1455 / 2720699
Applicant/Proprietor	
Hale BioPharma Ventures, LLC	

Extension of time limit pursuant to Rule 132(2) EPC

Examination procedure

With reference to your request, the time limit for replying to the communication pursuant to Article 94(3) EPC dated 05.07.16 has been extended

by 2 months

to a total of 6 months

from the date of notification of the above-mentioned communication.

Please note: To the extent that your request exceeded the above extension, your request has been refused.

Note
The granting of extensions to time limits is governed by the Implementing Regulations to the EPC and the Guidelines for Examination in the EPO, E-VII, 1.6. A request for extension, which would result in the total period set exceeding six months, must be reasoned and supported by evidence.

If no reply to the communication is received in due time, the European patent application will be deemed to be withdrawn (Art. 94(4) EPC).

Important information in case of a PACE request
If a PACE request has been validly filed for the application, the applicant is herewith informed that with the grant of the request for extension of time limit the application is removed from the PACE programme. A second PACE request for that application during the same stage of the procedure will not be processed (see OJ EPO 2015, A93, point 4).

For the Examining Division

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12 January 2017

European Patent Application 12 801 372.9-1455 based on PCT/US2012/042311
Title: Administration of benzodiazepine
Applicant: Hale BioPharma Ventures, LLC
Our ref.: EPA-124 519

In response to the Communication pursuant to Article 94(3) EPC dated 5 July 2016:

I Requests

1 It is requested to base the further examination on:

- the revised set of claims 1-14 submitted herewith (replacing previous claims 1-15 as on file); and
- original specification pages and figures. It is requested to defer any adaptions of the specification until the claims are considered allowable.

2 Should the application not be considered allowable, it is requested to issue another Communication according to Article 94(3) EPC. In particular, in light of decision G 1/10 and the procedure under current Rules 71(3) and (6) EPC, it is respectfully requested that the Examining Division refrains from effecting any amendments when issuing a Communication under Rule 71(3) EPC without the prior consent of the Applicant.

3 Purely as a matter of precaution, we request that oral proceedings under Article 116 EPC be held only in the event that the Examining Division intends to refuse the

application. However, if the hearing should take place either in The Hague or in Berlin, it is respectfully requested that a date for the oral proceedings be set allowing that same can be held by video-conference. In this case, the representative intends to use IP technology.

II Amendments (Article 123(2) EPC)

1 Claim 1 has been clarified to refer to the nasal administration of the pharmaceutical solution as kindly suggested by the Examining Division. Furthermore, former claim 7 was included into claim 1. The combined amounts of ethanol and benzyl alcohol in claim 1 have been adapted in view of this amendment.

2 The below table shows support for all claims:

Claim No.	Basis in PCT/US2012/042311 as filed
1	[010], [011], [072], [083], [084], original claims 1, 8, 10, 33
2	[010], [011], [022], [079], [085]-[0133], [0173], original claim 3
3	[010], [011], [022], [035]-[039], [043], [057], [079], [091]-[096], [0112], [0118], [0154], [0155]
4	[010], [011], original claim 5, 28
5	[010], [011], original claim 6, 29
6	[010], [011], [014], [023], [044], [058], [0138], Original claim 7, 30
7	[010], original claim 11
8	[017], [026], [047], [061], original claim 13, 36
9	[010], [011], original claim 17, 56, 57, 60
10	[010], original claim 18, 19, 49, 50
11	[010], [011], original claim 19, 22, 51, 54, 56, 57-62
12	Original claim 21, 22, 57, 58,
13	[010], [011], original claim 22, 54, 56, 57, 60
14	Original claim 22, 54

3 Applicant submits that the requirement of Article 123(2) EPC is met by the amended subject-matter of the claims.

III Novelty (Article 54 EPC)

The Examining Division takes the position that D6 discloses the particular combination of ethanol and benzyl alcohol, since the disclosure of paragraph [0039] of D6 encompasses this possible combination.

However, there is no *direct and unambiguous* mention of this particular combination in individualized form in D6, let alone in the claimed amounts.

Rather, paragraph [0039] of D6 encompasses the use of

- only one alcohol,
- the use of ethanol in combination with alcohols other than benzyl alcohol,
- the use benzyl alcohol in combination with alcohols other than ethanol, and
- combinations without ethanol or benzyl alcohol (e.g., propyl alcohol + butyl alcohol).

In order to arrive at the claimed combination, two selections from the lists of alcohols are required. To forestall an objection that the list in D6 only includes 8 members, it is submitted that the length of a list (EPO Guidelines, Part G, VI, 8(i) mention "a list having a certain length") is not relevant:

As set forth in T 946/06 (Reasons 2.3):

> *„However, the length of a list of alternatives is not a decisive criteria for the assessment of novelty, since even two short lists can result in multiple combinations and do not specifically disclose a particular individualised combination (decision T 7/86, point 5.1, OJ EPO 1988, 381).*"

As D6 does not disclose the particular combination of ethanol and benzyl alcohol in individualized form, Applicant submits that the claims possess novelty with respect to D6.

In view of the above facts and arguments, Applicant submits that the requirement of Article 54 EPC is met by the claimed subject-matter.

IV Inventive Step (Article 56 EPC)

The Search Opinion asserts a lack of inventive step between claims 1-14 of the present application, and reference D6.

Applicant submits that, aside from the previously mentioned Agarwal et al. publication, there is additional evidence in the published literature to establish inventive step.

The previously submitted Agarwal et al. publication demonstrates a surprising technical feature of the claimed combination. The pharmacokinetic (PK) study described by Agarwal et al., which demonstrated that the intranasal solution, which is a benzyl alcohol, ethanol solution falling within the current set of claims, demonstrated a high degree of bioavailability and was well-tolerated with only mild adverse events reported. Agarwal et al. at p. 367, column 1. Agarwal et al. stated, for example, that administration of intranasal diazepam did not appear to cause epistaxis (nose bleed), despite poor tolerability of previous intranasal formulation.

Ivaturi et al. ("Pharmacokinetics and tolerability of intranasal diazepam and midazolam in healthy adult volunteers," Acta Nurol. Scand. 2009:120: 353-357), as filed herewith, describes such a "previous intranasal formulation" with poor tolerability, i.e. a supersaturated solution containing 40 mg/ml diazepam, glycofurol, and water. Id., p. 354. Tolerability was reported on a 0-10 scale (0 = no change from normal; 10 = maximum intolerability), at various intervals after administration (0, 5, 15, and 60 min, and 8 hr. after administration). Id. The mean tolerability scores were 4.4 and 4.7 for the 5 and 10 mg doses, respectively. Id.

Therefore, the submitted evidence shows that the prior art intranasal formulation (at least some) were irritating, while a solution containing the claimed combination of alcohols (irrespective of any additional ingredients), was not irritating.

It is requested to acknowledge that the claimed combination of alcohols, hence, provides an improvement over the prior art. Since there is no teaching in the prior art regarding how to solve the technical problem of providing an improved intranasal solution, the claimed subject-matter was not obvious.

Therefore, Applicants submit that combining ethanol and benzyl alcohols to produce an intranasal product that provides superior drug exposure yet is non-irritating was not obviously deducible based on the available prior art.

In the event that the Examining Division does not acknowledge an improvement, it is – auxiliarily- submitted that also in this case an inventive step has to be acknowledged:

Considering the evidence provided by Agarwal, the claimed intranasal solution comprising ethanol and benzylalcohol has at least to be considered as being tolerable.

The underlying technical problem can therefore be formulated on a less ambitious basis as providing an intranasal solution, which is an alternative to the prior art solutions and which is also tolerable.

Sonne (US 6,193,985, enclosed herewith) teaches that addition of co-solvents such as ethanol is less desired, since such solutions "tend to be irritating to certain mucosal tissues." Col. 3, lines 1-4 and 65-67.

Thus, the bulk of Sonne's description relates to preparation of emulsions, which necessarily include oil and water. See col. 4, line 1 through col. 7, line 12 and Examples 1-3, 5-10, 15, 17, 19, 21. Indeed, consistent with Sonne's general teaching at column 3, lines 65-67, none of the Examples taught by Sonne suggest nasal administration of a benzodiazepine drug formulation that contains only tocopherol or tocotrienol, an alcohol and optionally an alkylglycoside.

Sonne teaches specific benzodiazepine formulations in Examples 1-3, 7-11, 17-19 and 22-23. Of these, Examples 1-3, 7-11, 17, 19 and 22-23 each describe an oil-in-water emulsion of the benzodiazepine. Such emulsions are specifically excluded from the instant claims, which recite solutions (not emulsions) and exclude any ingredients (such as water and oil) not included within the group of benzodiazepine drugs, tocopherols or tocotrienols, alcohols or glycols, and optionally alkyglycosides. Of the remaining examples, Example 18 is a solution of alprazolam in α-tocopherol in sesame oil for oral administration. Thus, each of the benzodiazepine compositions taught by Sonne contains oil in some form or another.

Accordingly, Sonne clearly teaches away from using ethanol. In other words, there was no reasonable expectation of success that the claimed combination of ethanol and benzyl alcohol can provide tolerable intranasal solutions.

In view of the above facts and arguments, Applicant submits that the requirement of Article 56 EPC is met by the claimed subject-matter.

V Summary and Final Remarks

1 In summary, Applicant submits that the claimed subject-matter meets the patentability requirements of the EPC.

2 Should there remain any issues that can be resolved by an informal call, the Examiner is kindly invited to contact the undersigned over the telephone.

3 Also, the Examining Division is respectfully requested to telephone the undersigned or to issue a further Examination Report if the Examining Division is minded to issue a Communication under Rule 71(3) EPC but wishes to propose amendments to the claims or the specification.

Dr. Hendrik Wichmann
European Patent Attorney

Enclosures
Amended set of claims 1-14 (marked-up version and clean copy);
Ivaturi et al. ("Pharmacokinetics and tolerability of intranasal diazepam and midazolam in healthy adult volunteers," Acta Nurol. Scand. 2009: 120: 353-357), and
Sonne (US 6,193,985)

US006193985B1

(12) **United States Patent**
Sonne

(10) **Patent No.: US 6,193,985 B1**
(45) **Date of Patent: *Feb. 27, 2001**

(54) **TOCOPHEROL COMPOSITIONS FOR DELIVERY OF BIOLOGICALLY ACTIVE AGENTS**

(75) Inventor: **Mette Rydahl Sonne**, Brøndby Strand (DK)

(73) Assignee: **A/S Dumex (Dumex Ltd)**, Copenhagen (DK)

(*) Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **08/856,054**

(22) Filed: **May 14, 1997**

Related U.S. Application Data

(63) Continuation of application No. 08/441,759, filed on May 16, 1995, now abandoned.

(30) **Foreign Application Priority Data**

May 16, 1994 (GB) 9409778

(51) **Int. Cl.**[7] **A61K 9/00**; A61K 9/107

(52) **U.S. Cl.** **424/400**; 424/439; 424/484; 424/486; 514/772

(58) **Field of Search** 424/439, 450, 424/485, 486, 400, 484; 514/772

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WO 91/16929	11/1991	(WO) .
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Lau et al.; "Absorption of diazepam and lorazepam following intranasal administration"; *International Journal of Pharmaceutics*; 54 (1989) pp. 171–174.

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Primary Examiner—Jeffrey C. Mullis
(74) *Attorney, Agent, or Firm*—Watov & Kipnes, P.C.; Allen R. Kipnes

(57) **ABSTRACT**

The present invention provides the use of a tocopherol or a derivative thereof as a solvent and/or emulsifier for substantially insoluble and sparingly soluble biologically active agents, especially in the manufacture of pharmaceutical compositions. Such compositions are particularly suitable for transmucosal, and especially intranasal or rectal administration, or administration via the oral cavity.

30 Claims, 2 Drawing Sheets

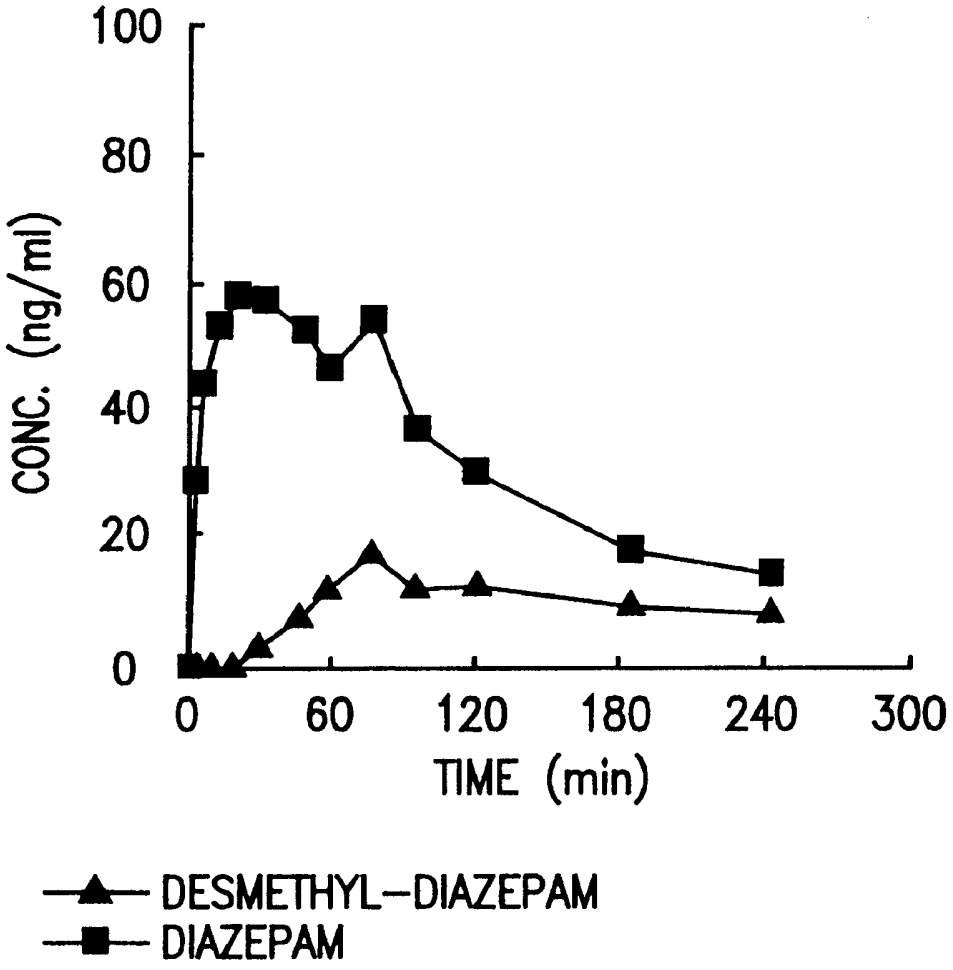
100
80
60
40
20
0
CONC. (ng/ml)
0
60
120
180
240
300
TIME (min)
DESMETHYL-DIAZEPAM
DIAZEPAM

FIG. 1

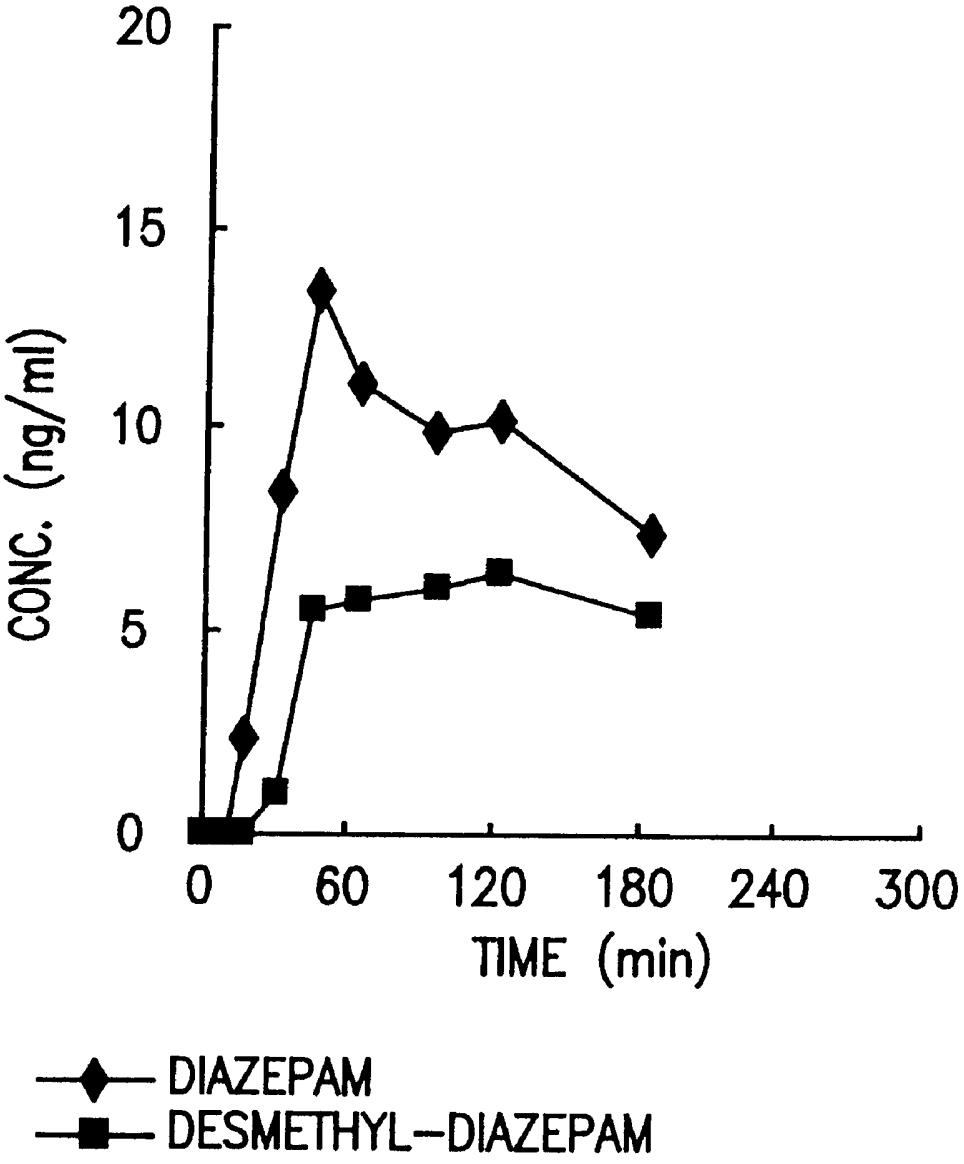
20
15
10
5
0
CONC. (ng/ml)
0
60
120
180
240
300
TIME (min)
DIAZEPAM
DESMETHYL–DIAZEPAM

FIG. 2

TOCOPHEROL COMPOSITIONS FOR DELIVERY OF BIOLOGICALLY ACTIVE AGENTS

This is a continuation application of U.S. Ser. No. 08/441,759 filed on May 16, 1995 now abandoned.

The present invention is directed to new pharmaceutical compositions for delivery of biologically active agents. More particularly, the invention concerns the use of a tocopherol or a derivative thereof to prepare compositions having low irritability suitable for administration to mucosal membranes and which may be used efficiently to administer drugs, which are substantially insoluble or only sparingly soluble in water.

For systemic action, drugs are normally administered by mouth and are then absorbed in the gastrointestinal tract. However, this mode of administration is not suitable in all circumstances, for example in the case of drugs which are metabolised to any significant degree by the liver or which are poorly absorbed. In other cases, the oral route may be impractical, for example in patients suffering from nausea or who are unconscious. Before surgery, oral administration is not advisable because of the risk of vomiting and in many cases, a more rapid effect may be required than can be achieved by the oral route.

In these circumstances the parenteral route is frequently used, most notably intravenous or intramuscular injection. However, whilst this provides a convenient way of achieving a strong and rapid systemic effect, it has a number of disadvantages including the requirement for sterile equipment and trained personnel. It is also unpleasant to the patient.

Moreover, in cases where a systemic effect is not required, local administration may be preferable, for example to avoid side effects, to reduce the dosage, or simply to facilitate the administration.

Such problems have lead in recent years to an increasing interest in developing formulations for the topical administration of drugs, and in particular for topical administration involving absorption from mucous membranes.

Topical administration has the advantage that drugs may be administered readily and simply to achieve a systemic or dermal, regional or localised effect, as required. However, topical absorption of drugs through the skin can be slow, and in many cases transmucosal routes of delivery are preferred. Since it may be performed by untrained personnel and permits therapeutic plasma levels of drugs rapidly to be achieved, intranasal administration has received particular attention in this regard.

For topical delivery, biologically active drugs are normally administered in the form of aqueous solutions. However, many biologically active compounds are substantially insoluble or only sparingly soluble in water and in such cases, organic solvents are required to dissolve these agents. The problem here is that mucosal tissues are generally very sensitive and such solvents are frequently too irritant to be of clinical use. Thus for example, Lau and Slattery [Int. J. Pharm. 1989, p. 171–74] attempted to administer the benzodiazepines diazepam and lorazepam by dissolving these compounds in a range of solvents including: triacetin, DMSO, PEG 400, Cremophor EL, Lipal-9-LA, isopropyladipate and azone dodecyle-aza-cycloheptane-2-one. Whilst many of the solvents dissolved diazepam and lorazepam in the desired concentrations, when administered to the nose they were too irritant to be of use. Thus, Cremophor EL was found to be the least irritative for mucosal tissue, but nasal absorption using this solvent is rather slow and peak concentration is low relative to that found after iv. administration.

Triglycerides such as vegetable oils are generally non-irritant, but usually these oils are too poor as solvents to be of any use.

Attempts have been made to develop various other vehicles for transmucosal delivery of drugs, such as benzodiazepines, having limited water solubility. Thus, for example WO 86/04233 of Riker discloses a pharmaceutical composition wherein the drug (eg. diazepam) is dissolved in a mixture of propellant and co-solvent eg. glycerolphosphatide. The composition requires a pressurized system and at least one halogenated hydrocarbon aerosol propellant.

In U.S. Pat. No. 4,863,720 of Burghardt, a sublingual sprayable pharmaceutical preparation is disclosed, in which the active drug can be a benzodiazepine, optionally comprising polyethylene glycol (PEG) and requiring ethanol, di- and/or triglyceride of fatty acids and a pharmaceutically acceptable propellant gas.

U.S. Pat. No. 4,950,664 of Rugby-Darby describes the nasal administration of benzodiazepines in a pharmaceutically acceptable nasal carrier. The carrier may be a saline solution, an alcohol, a glycol, a glycol ether or mixtures thereof.

In PCT WO 91/16929 of Novo Nordisk, glycofurols or ethylene glycols are suggested as carriers for a variety of drugs, including benzodiazepines, which may be used on mucous membranes.

Another solution proposed to this problem, has been the use of micelles or liposomes, but these are frequently difficult to produce on a technical scale.

A further constraint concerning nasal administration is that a small administration volume is required; it is not generally possible to administer more than about 0.1 ml per dose per nostril. Therefore, a great need exists for solvents, in which, on the one hand the solubility of the active drug is high, and which, on the other hand, are non-irritating to the mucosa.

The aim of the present invention is to provide a solution to the above mentioned problems.

Tocopherols and their derivatives such as esters for example, are widely used in vitamin supplementation and as antioxidants in the food industry and in many pharmaceutical compositions. However, although in a few cases, a potential use in formulating pharmaceutical compositions has been reported, tocopherols and derivatives thereof have not generally previously been proposed as drug carriers.

Thus for example, European Patent Application No. 539,215 of Stafford-Miller suggests a possible use of Vitamin E and its derivatives as penetration enhancers in topical compositions.

WO 89/03689 of The Liposome Co., describes a liposome system based on acid derivatives of α-tocopherol in a low pH aqueous medium for delivery of drugs which tolerate, or require, acid conditions.

The present invention is based on the surprising observation that tocopherols and derivatives thereof are excellent solvents for drugs which are substantially insoluble or sparingly soluble in water, whilst at the same time having a very low irritative potential for mucosal tissues.

As will be described in more detail below, it has also been found that certain tocopherol derivatives are efficient, non-irritant emulsifiers for such drugs, when dissolved in a tocopherol-based solvent.

In one aspect, the present invention thus provides the use of a tocopherol or a derivative thereof as a solvent and/or emulsifier for substantially insoluble and sparingly soluble biologically active agents, especially in the manufacture of pharmaceutical compositions.

A further aspect of the invention provides a composition for delivery of a substantially insoluble or sparingly soluble biologically active agent, comprising said agent dissolved in a tocopherol or a derivative thereof.

Tocopherols are a range of natural and synthetic compounds, also known by the generic term Vitamin E. α-Tocopherol (chemical name: 2,5,7,8-tetramethyl-2-(4',8', 12'-trimethyldecyl)-6-chromanole) is the most active and widely distributed in nature, and has been the most widely studied. Other members of the class include beta, gamma, and delta tocopherols but these are not used in pure form in therapeutics, although they are present in foodstuffs. Tocopherols occur in a number of isomeric forms, the D and DL forms being most widely available.

As used herein, the term "tocopherol" includes all such natural and synthetic tocopherol or Vitamin E compounds.

The melting point of natural α-tocopherol is between 2.5 and 3.5° C. α-Tocopherol is a viscous oil at room temperature, is soluble in most organic solvents, but insoluble in water.

Although tocopherols are available naturally in foodstuffs and may be extracted from plants, α-tocopherol is now mainly produced synthetically.

Any of the forms or isomers of tocopherols and their derivatives, eg. esters may be used according to the present invention. Thus for example, α-tocopherol can be used as such or in the form of its esters such as α-tocopherol acetate, linoleate, nicotinate or hemi succinate-ester, many of which are available commercially.

A special article of commerce is called Tenox GT-2 and consists of 70% tocopherol of natural origin, which has been concentrated from vegetable oil. This oil has a mild odour and a gentle taste.

The compositions of the present invention are particularly suited for application to mucous membranes in animals or humans, to deliver systemically substantially insoluble or sparingly soluble biologically active agents in a manner which ensures that a clinical effect is reached at least as rapidly as by conventional oral administration, with for instance tablets.

Thus, the compositions of the invention may be used for controlled release delivery of bioactive agents to achieve a beneficial or therapeutic effect over a prolonged period of time.

The compositions of the invention may also be applied to achieve a local effect, where desired, on the mucous membranes or the underlying tissue.

However, whilst the beneficial effects of the invention are particularly apparent in transmucosal delivery, the utility of the invention is not limited and compositions according to the invention may also be administered topically to all body surfaces, including the skin and all other epithelial or serosal surfaces, as well as parenterally or enterally, eg. as implants or by intravenous, intramuscular or subcutaneous injection, by infusion, or orally.

Transmucosal delivery is preferred however, and compositions according to the invention may be administered to mucosal membranes for example in the nose, vagina, rectum, ears, eyes, oral cavity, lungs, genito-urinary tracts, and gastro-intestinal tract. Nasal, rectal and oral cavity administrations are particularly preferred.

The compositions of the invention may be used directly as solutions of the bioactive agent in the tocopherol solvent. However such solutions are viscous, and the viscosity may be too high for certain applications, for example to achieve a sprayable formulation for nasal application.

Viscosity can be reduced by addition of co-solvents such as ethanol, but this is less desired, since solutions of this kind tend to be irritating to certain mucosal tissues.

Alternatively, the tocopherol solutions may be emulsified, to obtain formulations of lower viscosity. This may be achieved in known manner, by mixing the tocopherol-based "oil phase" containing the dissolved bioactive agent with an appropriate aqueous phase, eg. water, saline or buffer solutions.

Methods and appropriate aqueous media for obtaining emulsions are well known in the art and described in the literature. Emulsions according to the invention may be oil-in-water (O/W) or water-in-oil (W/O) emulsions. Generally speaking, O/W emulsions may be achieved when the oil phase contains up to about 70% lipids. W/O emulsions are formed when the oil phase exceeds c.a. 70%.

For nasal administration, due to the small administration volume required, it has generally been found that a high concentration of the oil (or lipid) phase is required. Emulsions with high lipid content are technically difficult to achieve and may be unstable. It may therefore be necessary to employ an emulsifier in order to form a stable emulsion. A wide range of emulsifiers are well known, both in the food and pharmaceutical arts, and are widely described in the literature. However, stability and viscosity may still be a problem, where very high contents of the oil phase are required. Moreover, some of the more widely available commercial emulsifiers, eg. phospholipids, polysorbates or various sorbitan esters of fatty acids may be irritating to the more sensitive mucosal tissues, such as those of the nose.

The inventors have surprisingly found however that tocopherol derivatives, particularly certain esters, may themselves form efficient, non-irritating emulsifiers to enable stable emulsions to be formed, even where high lipid levels are involved eg. about 50–70%. Particular mention may be made in this regard of Vitamin E TPGS which is a water soluble derivative of Vitamin E and consists of α-tocopherol, which is esterified with succinic acid, the other acidic group of the latter being esterified with polyethylene glycol 1000. Vitamin E TPGS is an almost odourless waxy amphiphilic substance with a molecular weight about 1513. The melting point is about 36° C. and its solubility in water is about 20%.

Stable emulsions may readily be achieved according to the invention using a range of tocopherols or derivative compounds as solvents, with Vitamin E TPGS as emulsifier, and any suitable aqueous medium.

A further aspect of the invention thus provides a composition suitable for delivery of substantially insoluble or sparingly soluble biologically active agents, comprising a tocopherol or a derivative thereof, and Vitamin E TPGS as emulsifier.

The tocopherol derivative emulsifier of the invention may be used alone or in conjunction with other known emulsifiers eg. phospholipids, polysorbates, sorbitan esters of fatty acids, cetearyl glucoside or poloxamers.

It has furthermore surprisingly been shown that various other solvents may be used in the emulsion system described above, without compromising the stability of the emulsion.

When the emulsion according to the present invention is of the oil-in-water type, it is desirable that the droplet size is as small as possible. It has been shown that by using systems according to the invention, for example, α-tocopherol, water, Vitamin E TPGS and bioactive agent, it is possible to form stable emulsions with an initial droplet size in the range 0.01–100 pm, preferably 0.01–50 μm, most preferably 0.1–20 μm.

The compositions which may be prepared according to the present invention, may contain any biologically active agent which is insoluble or sparingly soluble in water, ie.

with a solubility in water (w/v) which is 3% or less. For example such agents may include any bioactive agent which has less than 1% (w/v) solubility in water. Representative active agents from a range of different therapeutic groups are listed below, by way of exemplification.

Hormones and hormone-like substances of the steroid-group:

Corticosteroids such as cortisone, hydrocortisone, prednolone, prednisolone, triamcinolone acetonide, dexamethasone, flunisolide, budesonide, toxicorole pivalate, betametasone, beclomethasone dipropionate, fluticasone etc;

Sex-hormones such as: estradiol, progesterone, testosterone etc;

Antibiotics: Tetracyclines such as tetracycline, doxycycline, oxytetracycline, chloramphenicol etc; Macrolides such as erythromycin and derivatives, etc;

Antivirals: such as acyclovir, idoxuridine, tromantadine etc;

Antimycotics: Miconazole, ketoconazole, fluconazole, itraconazole, econazole, terconazole, griseofulvin, and polyenes such as amphotericin B or nystatine etc;

Anti-amoebics: Metronidazole, metronidazole benzoate and tinidazole etc;

Anti-inflammatory drugs: NSAID's such as indomethacin, ibuprofen, piroxicam, diclofenac etc;

Anti-allergics: Disodium cromoglycate etc;

Immunosuppressive agents: cyclosporins etc;

Coronary drugs: including vasodilators such as nitroglycerin, isosorbide dinitrate, Calcium-antagonists such as verapamile, nifedipine and diltiazem, Cardiac-glycosides such as digoxine.

Analgesics: eg. morphine, buprenorphine, etc;

Local anaesthetics: eg. lidocaine, etc;

Anxiolytics, sedatives & hypnotics: diazepam, nitrazepam, flurazepam, estazolam, flunitrazepam, triazolam, alprazolam, midazolam, temazepam, lormetazepam, brotizolam, clobazam, clonazepam, lorazepam, oxazepam, buspirone, etc;

Migraine relieving agents: sumatriptan, ergotamines and derivatives etc;

Drugs against motion sickness: eg. cinnarizine, anti-histamines, etc;

Anti-emetics: eg. ondansetron, tropisetron, granisetrone, metoclopramide, etc.

Others: such as disulfiram, vitamin K, etc.

The emulsions according to the present invention are especially suitable for nasal application because of their low index of irritability and are therefore particularly well suited to the delivery of biologically active drugs influencing the central nervous system (CNS).

Other biologically active agents which may be used include peptides, hormones, etc. The active substance may be present in an amount of from about 0.0001% to 50% of the total composition, preferably 0.001% to 40% (w/w).

Generally speaking compositions of the invention may contain from 1 to 99.99% (w/w), preferably 20 to 99.99%, most preferably 40 to 99.99% (w/w) of the tocopherol or tocopherol derivative solvent. The emulsion used in compositions of the invention may contain 1 to 95% (w/w) of the tocopherol or derivative thereof, preferably 20 to 95% (w/w), most preferably 35 to 80% (w/w).

As mentioned above, the emulsions of the present invention can be prepared by conventional means, by heating the oil and aqueous phases separately, and then mixing the two phases. The active ingredient can be dissolved in the lipid fraction of the tocopherol solvent and other solvents may be added if desired. The emulsifier, eg. Vitamin E TPGS, and optionally other emulsifiers, can be added to either the oil and/or the water phase. The water phase is then vigorously mixed with the oil phase. Mixing, eg. stirring may be continued as required eg. for up to 2 hours. Depending on the viscosity of the emulsion, a magnetic stirrer, a low shear mixer or the like can be used. If necessary, the emulsion can be processed by a low shear mixer and a high pressure homogenizer to achieve the desired droplet size. The formulations may be inspected microscopically to measure the droplet size and to be sure that no precipitation has taken place. The type of emulsion formed may be determined readily by a colour test using an oil- and/or water-soluble dye. To confirm the result, it may be examined whether the emulsion is easy to wash off with water or not. An O/W emulsion is coloured with the water-soluble dye and is very easy to wash off with water. A W/O emulsion is coloured with the oil-soluble dye and is very difficult to wash off with water.

In a further aspect, the present invention thus provides a method of preparing a composition for delivery of a substantially insoluble or sparingly soluble biologically active agent, said method comprising dissolving said agent in an amount of a tocopherol or a derivative thereof, sufficient to dissolve said agent.

In a preferred aspect, the method of the invention further comprises forming an emulsion of said tocopherol/biologically active agent solution, by mixing with an aqueous phase, optionally in the presence of an emulsifier, preferably vitamin E TPGS.

The compositions of the invention may take any of the conventional pharmaceutical forms known in the art, and may be formulated in conventional manner, optionally with one or more pharmaceutically acceptable carriers or excipients. Thus for example the compositions may take the form of ointments, creams, solutions, salves, emulsions, lotions, liniments, aerosols, sprays, drops, pessaries, suppositories, tablets, capsules or lozenges.

In a still further aspect, the present invention provides the use of a tocopherol or a derivative thereof for the preparation of a composition for delivery of a substantially insoluble or sparingly soluble biologically active agent to a human or non-human animal subject.

Alternatively viewed, the invention can be seen to provide a method of treatment of a human or non-human animal subject by delivery of a substantially insoluble or sparingly soluble biologically active agent, said method comprising administering to said subject a composition of the invention as hereinbefore defined.

The formulations according to the invention may be optimized with respect to bioadhesion, sprayability and viscosity, as desired. Thus for example, the following co-solvents may be added:

Vegetable oils such as sesame- or olive- or fractionated coconut oil, alcohols such as ethanol, propylene glycol, glycerol, polyethylene glycol or benzyl alcohol; or triacetin.

To optimize the stability of the emulsions, it may be appropriate to add surfactants such as Vitamin E TPGS poloxamers (eg. Pluronic®), cetearyl glucoside, polysorbates or sorbitan esters of fatty acids, or any of the other surfactants well known in the art, or other stabilisers such as xanthan gum, or propylene glycol alginate.

It is also possible to enhance the bioadhesive properties of the formulations according to the present invention by addition of bioadhesive polymers such as:

polyacrylic polymers such as carbomer and carbomer derivatives, eg. Polycarbophil or Carbopol etc;

cellulose derivatives such as hydroxymethyl-cellulose, hydroxyethylcellulose, hydroxypropyl-cellulose or sodium carboxymethylcellulose etc;

natural polymers like gelatin, sodium alginate, pectin etc;

more generally, any physiologically acceptable polymer showing bioadhesive characteristics may be used.

To ensure that the formulations have a reasonable shelf-life it may be desirable to include preservatives such as benzalkonium chloride, sodium edetate, sorbic acid, potassium sorbate, phenoxyethanol, phenetanol, parabens or others known in the art. Addition of odour- or taste-masking compounds can also be desirable.

The invention will now be described in more detail in the following non-limiting Examples, with reference to the drawings in which:

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graph showing mean serum concentrations (ng/ml) against time (minutes) after intranasal administration of 2.5 mg diazepam (Formulation C) -▲- Desmethyldiazepam -■- Diazepam;

FIG. 2 is a graph showing mean serum concentrations (ng/ml) against time (minutes) after oral administration of 2.0 mg diazepam (Formulation D) -■- Desmethyldiazepam -◆- Diazepam;

EXAMPLES

As already mentioned, administration of drugs with very low water solubility to the nose is difficult, because of the limited volume which is acceptable for the nose (about 100 μl). The first example has a very high concentration of diazepam, and it is possible to administrate diazepam to the nose and to achieve a rapid clinical effect.

Example 1

A diazepam nosedrop preparation is made as follows: (100 g)

5 g of diazepam is mixed with 44 g of Tenox GT2, and 22 g of triacetin, and 5 g of Vitamin E TPGS. The oil phase is heated slowly to a homogeneous phase is achieved. To the water phase, 1.45 g of Pluronic F-68 (poloxamer 188) and 0.01 g of benzalkonium chloride are added, the water phase is heated slowly to a homogeneous phase is achieved. The water phase is vigorously mixed into the oil phase by using a magnetic stirrer. Thereafter, the emulsion is cooled to room temperature still on the magnetic stirrer. The emulsion was a pale yellow o/w emulsion, where the mean droplet size was about 1–2 μm.

This formulation (1) was tested in 8 rabbits in a randomized cross-over study compared with a commercially available diazepam formulation, Stesolido 5mg/ml for injection, (2).

Formulation 1 was given intranasally (i.n.) with a Eppendorf Multipette® 4780. Each rabbit was held in a supine position during and one minute after i.n. dosing in one nostril. The rabbits receive a volume that equals 2 mg diazepam, 40% of formulation 1. After each administration the actual dose received is estimated by visual inspection of the pipette tip and the rabbit nostrils. Only applications volumes estimated to 80% are accepted.

Formulation 2 was given as an ear-vein infusion during M minute. The rabbits received 0.4 ml Stesolid® 5 mg/ml (equals 2 mg diazepam). The rabbits were placed in a supine position for half a minute to attain the same experimental conditions as for i.n. dosing.

The rabbits were then tested with respect to pharmacodynamic response in the following way:

Hind legs to one side and the rabbit must stay in this position even after a firm tip with a finger on the hip. The test is immediately repeated with both legs placed on the other side.

The rabbits were tested approximately once per minute until positive pharmacodynamic response, and thereafter tested every 2 minutes. Total test period is 20 minutes. The same person has dosed and tested all the rabbits in the present study.

The time to pharmacodynamic response is 4.4 minutes (mean, n=8) using formulation 1 and 1.6 minutes (mean, n=8) using formulation 2.

Example 2

A diazepam nosedrop preparation is made as follows: (100 g)

5 g of diazepam is mixed with 45.4 g of Tenox GT2, and 22.7 g of triacetin, and 15 g of Vitamin E TPGS. The oil phase is heated slowly to a homogeneous phase is achieved. To the water phase, 1.45 g of Pluronic F-68 (poloxamer 188) and 0.01 g of benzalkonium chloride are added, the water phase is heated slowly to a homogeneous phase is achieved. The water phase is vigorously mixed to the oil phase by using a magnetic stirrer. Thereafter, the emulsion is cooled to room temperature still on the magnetic stirrer. The emulsion is a clear orange w/o emulsion.

A less concentrated formulation of diazepam is required for the rectal administration, but still it can be very difficult to find an acceptable vehicle with low irritation.

Example 3

A diazepam enema preparation is made as follows: (100 g)

1 g of diazepam is mixed with 40 g of (-tocopherol, and 15 g of Vitamin E TPGS. The oil phase is heated slowly to a homogeneous phase is achieved. 5 g of ethanol is added to the oil phase immediately before mixing with the water phase. To the water phase, 2.5 g of Pluronic F-68 (poloxamer 188), and 0.01 g of benzalkonium chloride, and 0.05 g of disodium edetate are added, the water phase is heated slowly to a homogeneous phase is achieved. The water phase is vigorously mixed to the oil phase by using a magnetic stirrer. Thereafter, the emulsion is cooled to room temperature still on the magnetic stirrer. The emulsion is a white o/w emulsion.

Cinnarizine is used for motion sickness. Like diazepam, the drug has a very low water solubility. It will be a great advantage if the patient can administer the drug easily and have a rapid effect.

Example 4

A cinnarizine nosedrop formulation is made as follows: (100 g)

5 g of cinnarizine is mixed with 64 g of α-tocopherol, and 8 g of Vitamin E TPGS. The oil phase is heated slowly to a homogeneous phase is achieved. To the water phase, 1.5 g of Pluronic F-68 (poloxamer 188), and 0.01 g of benzalkonium chloride, and 0.05 g of disodium edetate are added, the water phase is heated slowly to a homogeneous phase is achieved. The water phase is vigorously mixed to the oil phase by using a magnetic stirrer. Thereafter, the emulsion is cooled to room temperature still on the magnetic stirrer. The emulsion is a white o/w emulsion.

Miconazole is used for the local treatment of infections caused by fungi. The next two formulations show formulations for use in the oral cavity and the vagina.

Example 5

A miconazole preparation for the oral cavity is made as follows: (100 g)

20 g of miconazole is mixed with 58.8 g of α-tocopherol, and 13 g of Vitamin E TPGS. The oil phase is heated slowly to a homogeneous phase is achieved. 5 g of ethanol is added to the oil phase immediately before mixing with the water phase. To the water phase, 1.5 g of Pluronic F-68 (poloxamer 188), and 0.01 g of benzalkonium chloride, and 0.05 g of disodium edetate are added, the water phase is heated slowly to a homogeneous phase is achieved. The water phase is added very slowly to the oil phase under vigorously mixing by using a magnetic stirrer. Thereafter, the emulsion is cooled to room temperature still on the magnetic stirrer. The emulsion is a yellow to brown w/o emulsion.

Example 6

A miconazole vaginal cream is made as follows: (100 g)

5 g of miconazole is mixed with 38 g of α-tocopherol, and 38 g of Vitamin E TPGS. The oil phase is heated slowly to a homogeneous phase is achieved. To the water phase, 2.5 g of Pluronic F-681 (poloxamer 188) and 0.01 g of benzalkonium chloride, and 0.05 g of disodium edetate are added, the water phase is heated slowly to a homogeneous phase is achieved. The water phase is vigorously mixed to the oil phase by using a low shear mixer. Thereafter, the emulsion is cooled to room temperature still mixed by the low shear mixer. The emulsion is a glossy, beige w/o emulsion. The emulsion has a consistency as an ointment and is very sticky.

The following Examples are divided into three subsections covering 1) Solubility; 2) Compositions and 3) Pharmacology/toxicology.

Example 7

Solubility

For the following, non-limiting, sparingly soluble drugs in water, the solubility in α-tocopherol and sesame oil are listed in Table 1:

Sesame oil was chosen as the reference, because it is a very commonly used and well tolerated vegetable oil. The solubilities in sesame oil and α-tocopherol were investigated by visual inspection of the saturation point.

TABLE 1

Active agent	g drug in 100 g of α-tocopherol	g drug in 100 g of sesame oil
Diazepam	12	2
Alprazolam	4 <x< 6	<0.2
Midazolam	>13	1 <x< 2
Cinnarizine	11 <x< 18	2 <x< 4
Metoclopramide	2 <x< 4	<2
Budesonide	1 <x< 2	<0.1
Miconazole	60	5 <x< 10
Metronidazole benzoate	12 <x< 14	<2
Lidocaine	>45	>18
Disulfiram	5	3 <x< 4
Progesterone	>30	2 <x< 4
Testosterone	16 <x< 18	0.6 <x< 1

All the investigated biologically active agents show a surprisingly high solubility in α-tocopherol.

Compositions

In the following, non-limiting Examples, several drugs are shown in a number of different types of administration forms.

The emulsions were prepared as follows:

The oil and the water phase were heated slowly until homogeneous phases were achieved.

The warm water phase was vigorously mixed into the oil phase. Then, the emulsion was slowly cooled to room temperature while stirring. The emulsion may be homogenized.

The preparation of the solutions was made as simple solution, in which the preparations were stirred until the drug was completely dissolved.

As already mentioned, administration of drugs with low water solubility to the nose is very difficult, because of the limited acceptable volume for the nose (about 100 μl). The following examples have very high concentration of diazepam, so it was possible to administer diazepam to the nose and to get a fast clinical effect.

Example 8

An O/W emulsion of diazepam as a nosedrop (100 g):

Oil phase:	Diazepam	5.000 g
	α-Tocopherol	59.000 g
	Vitamin E TPGS.	5.000 g
Water phase:	Disodium edetate	0.050 g
	Potassium sorbate	0.200 g
	Xanthan gum	0.025 g
	purified water to	100.000 g

The water phase was adjusted to pH 4.7 by 1N HCl.

Example 9

An O/W emulsion of diazepam as nosedrop (100 g):

Oil phase:	Diazepam	5.000 g
	α-Tocopherol	58.000 g
	Sorbitan trioleate	0.500 g
	Fractionated coconut oil	5.000 g
Water phase:	Potassium sorbate	0.200 g
	Poloxamer 188	1.000 g
	Xanthan gum	0.030 g
	Polysorbate 80	0.500 g
	Purified water to	100.000 g.

The water phase was adjusted to pH 4.5 by 2N HCl.

Example 10

An O/W emulsion of diazepam as nosedrop (100 g):

Oil phase:	Diazepam	5.000 g
	α-Tocopherol	50.000 g
	Triacetin	10.000 g
	Cetearyl glucoside	2.000 g
	Methylparahydroxybenzoate (MPHB)	0.080 g
	Propylparahydroxybenzoate (MPHB)	0.040 g
Water phase:	Poloxamer 188	3.000 g
	Xanthan gum	0.030 g
	Purified water to	100.000 g.

Example 11

A solution of diazepam, eg. as nosedrop, (25 g):

Diazepam	1.250 g
α-Tocopherol	10.000 g
Triacetin	13.750 g

A less concentrated formulation of diazepam is needed for the rectal administration, but still it can be very difficult to find an acceptable vehicle with low irritation.

Example 12

A solution of cinnarizine, eg. as drops for administration to the oral cavity (25 g):

Cinnarizine	1.250 g
α-tocopherol	17.500 g
ethanol	1.250 g
fractionated coconut oil	5.00 g

A study has shown, that cinnarizine has a higher oral bioavailability, if it is dissolved in a vehicle before administration, [J. Pharm. Sci., vol 76, no. 4, p. 286–288, 1987], an example of such a vehicle could be α-tocopherol.

Example 13

A solution of cinnarizine, eg. for oral administration in capsules, (25 g):

Cinnarizine	0.750 g
α-Tocopherol	24.250 g

Miconazole is used locally for treatment of infections caused by fungi. The following examples show formulations for the oral cavity and the vagina.

Example 14

A solution of miconazole e. g. as drops for administration to the oral cavity (25 g).

Miconazole	6.250 g
α-Tocopherol	16.875 g
Ethanol	1.875 g

Budesonide is a very potential drug, and is used as a local corticoid, e. g. for rhinitis.

Example 15

An O/W emulsion of budesonide as nosedrop or nasal spray (50 g).

Oily phase:	Budesonide	0.025 g
	α-tocopherol	12.500 g
	Vitamin E TPGS	5.000 g
Water phase:	Potassium sorbate	0.100 g
	Xanthan gum	0.020 g
	Purified water to	100.000 g

The water phase is adjusted to pH 4.5 with 2N HCl.

Example 16

A solution of budesonide as nosedrop (25 g).

Budesonide	0.025 g
α-tocopherol	10.000 g
Sesame oil	14.975 g

Alprazolam is a benzodiazepine which is used for the treatment of e. g. anxiety, therefore a rapid effect is desired in a easy way.

Example 17

An o/w emulsion of alprazolam as nosedrop or nasal spray (100 g).

Oily phase:	Alprazolam	0.500 g
	α-tocopherol	20.000 g
	Vitamin E TPGS	10.00 g
Water phase:	Potassium sorbate	0.200 g
	Xanthan gum	0.050 g
	Purified water to	100.000 g

The water phase is adjusted to pH 4.5 with 2N HCl.

Example 18

A solution of alprazolam, e.g. as drops for administration in the oral cavity (25 g).

alprazolam	0.125 g
α-tocopherol	13.750 g
sesame oil	11.125 g

Midazolam is a benzodiazepine tranquiliser with a sedative effect e.g., and is used for the treatment of anxiety and tension states, and as a sedative and for premedication. Midazolam has a very high first-pass effect after oral administration.

Example 19

An O/W emulsion of midazolam as nosedrop (50 g).

Oily phase:	Midazolam	1.250 g
	α-Todopherol	29.500 g
	Vitamin E TPGS	2.500 g
Water phase:	Potassium sorbate	0.100 g
	Xanthan gum	0.013 g
	Poloxamer 188	0.750 g
	Disodium edetate	0.025 g
	Purified water to	100.000 g

The water phase is adjusted to pH 4.5 with 2N HCl.

Disulfiram is used in the treatment of chronic alcoholism.

Example 20

A solution of disulfiram, e. g. as an oral solution or for oral administration by capsules (25 g).

Disulfiram	1.125 g
α-Tocopherol	23.875 g

Example 21

An O/W emulsion of lidocaine for treatment of e.g. insect bites (100 g).

Oily phase:	Lidocaine	5.000 g
	α-Tocopherol	40.000 g
	Cetearyl glucoside	4.000 g
	MPHB	0.080 g
	PPHB	0.040 g
Water phase:	Poloxamer 188	3.000 g
	Xanthan gum	0.030 g
	Purified water to	100.000 g

Example 22

Pharmacology

Studies on Rabbits

Preparations containing CNS active and muscle relaxing drugs such as diazepam and midazolam were tested in a pharmacodynamic model in rabbits.

The model consists of the following tests:

Test 1:

Hind legs to one side and the rabbit must stay in this position even after a firm tip with a finger on the hip. The test is immediately repeated with both legs placed on the other side.

Test 2:

Hind legs stretched out backwards and the rabbit must stay in this position even after a firm tip with a finger on the hip.

Test 3:

The rabbit must stay in a supine position, when placed in such a position.

After administration of the formulations (i.n., oral or i.v.) the rabbits were exposed to the three tests approximately once per minute until positive pharmacodynamic response, and thereafter every 2 minutes. The total test period was 20 minutes after i.n. and i.v. administration and 30 minutes after peroral administration.

The time elapsed from administration until the first positive response in test 1 was used to compare the onset of action of the different formulations.

Study 1

This pharmacodynamic study compared the nasal formulation of Example 8 (C) containing 5% of diazepam to a commercially available diazepam formulation, Stesolido 2mg tablet, Dumex (D). The study was run in 8 rabbits in a randomized cross-over study. The rabbits were tested for pharmacodynamic response as described previously, but the test period was 30 minutes after peroral administration to be sure to obtain a pharmacodynamic effect.

Formulation C was given intranasally (i.n.) with a laboratory pipette. Each rabbit was held in a supine position during and one minute after i.n. dosing in one nostril. The rabbits received a volume equivalent to 2.5 mg diazepam. After each administration the actual dose received is calculated by subtraction of the weight of the pipette before and after administration. Only applications determined to 80% (2 mg diazepam) were accepted.

Formulation D was given as an oral administration using a stomach pump. The tablet was dissolved in 5 ml water immediately before administration. The tube was rinsed with 10 ml water.

The time to onset of pharmacodynamic response in test 1 is 4.5 minutes (median, n=7) using formulation C and 19.4 minutes (median, n=8) using formulation D.

Study 2

This pharmacokinetic study compared the nasal formulation of Example 8 (C) containing 5% of diazepam to a commercially available diazepam formulation, Stesolido 2mg tablet, Dumex (D). The study was run in 8 rabbits in a randomized cross-over study.

Formulation C was given intranasally (i.n.) as described in study 1.

Formulation D was given by oral administration as described in study 1 using a stomach pump.

Blood samples from the ear-vein were taken before administration (time=0) and at 2, 5, 10, 15, 30, 45, 60, 75, 90, 120, 180 and 240 minutes.

Serum was analyzed for diazepam and the metabolite, desmethyldiazepam using Gas Chromatografy (GC). The limit of detection was 5ng/ml for both substances.

The pharmacokinetic parameters found for diazepam were t_{max}=23 minutes (median, n=6), C_{max}=68.2 ng/ml (median, n=6) after administration of formulation C and t_{max}=45 minutes (median, n=6), C_{max}=9.7 ng/ml (median, n=6) after administration of formulation D.

FIGS. **1** and **2** illustrate the mean serum concentrations of diazepam and desmethyldiazepam after administration of formulations C and D.

Study 3

This pharmacodynamic study compared Example 8(C) containing 5% of diazepam with Example 19 (E) containing 2.5% of midazolam. The study was using 6 rabbits.

Formulations C and E were given intranasally (i.n.) with a laboratory pipette. Each rabbit was held in a supine position during and one minute after i.n. dosing in one nostril. The rabbits received a volume equivalent to 2.5 mg diazepam or 1.25 mg midazolam, respectively.

After each administration the actual dose received was calculated by subtraction of the weight of the pipette before and after administration. Only doses equivalent to 80% were accepted.

The time to onset of pharmacodynamic response in test 1 was 3.1 minutes (median, n=6) using formulation C containing diazepam and 2.5 minutes (median, n=6) using formulation E containing midazolam.

Example 23

Toxicology

Local Irritancy in Humans:

The investigation was carried out in order to estimate irritation after nasal application of 10 mg of diazepam; 100 mg of the preparation from Example 8 in each nostril.

6 volunteers, 3 male and 3 female participated in the trial.

The investigator inspected both nostrils macroscopically for local irritation at the following times: Immediately after medication, at 30 minutes, and 1, 2, 4, and 6 hours.

In one volunteer the macroscopic inspection showed light blush of both nostrils immediately after medication. None of the six volunteers had local irritation of the nostrils 30 minutes after application, see table 2.

Conclusion

The total results of the trial have shown that preparation of Example 8 does not cause unacceptable irritation of the nostrils.

TABLE 2

Individual local irritation of the nostrils after intranasal administration of 10 mg diazepam, (Example 8)

	Local irritation											
	Immediately after medication		30 min		1 h		2 h		4 h		6 h	
Volunteer no	R	L	R	L	R	L	R	L	R	L	R	L
1	—	—	—	—	—	—	—	—	—	—	—	—
2	—	—	—	—	—	—	—	—	—	—	—	—
3	—	—	—	—	—	—	—	—	—	—	—	—
4	Light blush	Light blush	—	—	—	—	—	—	—	—	—	—
5	—	—	—	—	—	—	—	—	—	—	—	—
6	—	—	—	—	—	—	—	—	—	—	—	—

R: right nostril
L: left nostril

What is claimed is:

1. A composition for the non-topical delivery of an active agent in the form of a non-liposomal emulsion comprising two phases:

a) a first tocopherol-based phase comprising an active agent which is no more than sparingly soluble in water and which is not a tocopherol; and

an amount of 20% to 95% w/w based on the total weight of the composition of at least one tocopherol or acetate, linoleate, nicotinate or hemi-succinate derivative thereof sufficient to dissolve the active agent in the tocopherol-based phase;

b) a second phase comprising an emulsifying agent wherein the emulsifying agent is vitamin E TPGS; wherein said active agent is selected from the group consisting of antibiotics; antivirals; antimycotics; anti-amoebics; non-steroidal anti-inflammatory drugs; anti-allergics; immunosurpressive agents; coronary drugs; analgesics, local anaesthetics; anxiolytics, sedatives and hypnotics; migraine relieving agents; drugs against motion sickness; anti-emetics; disulfiram and vitamin K.

2. A composition as claimed in claim 1 wherein the tocopherol is α-tocopherol or an acetate, linoleate, nicotinate or hemi-succinate derivative thereof.

3. A composition as claimed in claim 1 in a form suitable for transmucosal, peroral, enteral or parenteral application.

4. A composition as claimed in claim 1, in a form of suitable for intranasal, buccal, vaginal or rectal application or for administration via the oral cavity.

5. A composition as claimed in claim 1 wherein the active agent is selected from the group consisting of tetracycline, doxycycline, oxytetracylcline, chloramphenicol, erythromycin, acyclovir, idoxuridine, tromantadine, miconazole, ketoconazole, fluconazole, itraconazole, econazole, griseofulvin, amphotericin B, nystatine, metronidazole, metronidazole benzoate, tinidazole, indomethacin, ibuprofen, piroxicam, diclofenac, disodium cromoglycate, nitroglycerin, isosorbide dinitrate, verapamile, nifedipine, diltiazem, digoxine, morphine, cyclosporins, buprenorphine, lidocaine, diazepam, nitrazepam, flurazepam, estazolam, flunitrazepam, triazolam, alprazolam, midazolam, temazepam lormetazepam, brotizolam, clobazam, clonazepam, lorazepam, oxazepam, busiprone, sumatriptan, ergotamine derivatives, cinnarizine, anti-histamines, ondansetron, tropisetron, granisetrone, metoclopramide, disulfiram, and vitamin K.

6. A composition as claimed in claim 1, wherein the active agent is a coronary drug selected from the group consisting of vasodilators; calcium-antagonists and cardiac-glycosides.

7. A composition as claimed in claim 1, wherein the active agent is a benzodiazepine or an antimycotic.

8. A composition as claimed in claim 1, wherein the active agent is selected from the group consisting of diazepam, midazolam and miconazole.

9. A composition as claimed in claim 1, wherein the amount of the tocopherol or acetate, linoleate, nicotinate or hemi-succinate derivative thereof is from 35 to 80% (w/w).

10. A composition as claimed in claim 1, further comprising at least one additional component selected from the group consisting of solvents, surfactants, stabilizers, bioadhesive polymers, preservatives, odor-masking agents and taste-masking agents.

11. A composition for the non-topical delivery of an active agent in the form of a non-liposomal emulsion comprising two phases:

a) a first tocopherol-based phase comprising an active agent which is no more than sparingly soluble in water and which is not a tocopherol; and

an amount of 20% to 95% w/w based on the total weight of the composition of at least one tocopherol or acetate, linoleate, nicotinate or hemi-succinate derivative thereof sufficient to dissolve the active agent in the said tocopherol-based phase;

b) a second phase comprising an emulsifying agent wherein the emulsifying agent is vitamin E TPGS.

12. A composition as claimed in claim 11 wherein the active agent is selected from the group consisting of antibiotics; antivirals; antimycotics; anti-amoebics; non-steroidal anti-inflammatory drugs; anti-allergics; immunosuppressive agents; coronary drugs; analgesics; local anaesthetics; anxiolytics, sedatives and hypnotics; migraine relieving agents; drugs against motion sickness; anti-emetics; disulfiram and vitamin K.

13. A composition as claimed in claim 12 wherein the active agent is selected from the group consisting of tetracycline, doxycycline, oxytetracycline, chloramphenicol, erythromycin, acyclovir, idoxuridine, tromantadine, miconazole, ketoconazole, fluconazole, itraconazole, econazole, griseofulvin, amphotericin B, nystatine, metronidazole, metronidazole benzoate, tinidazole, indomethacin, ibuprofen, piroxicam, diclofenac, Disodium cromoglycate, nitroglycerin, isosorbide dinitrate, verapamile, nifedipine, diltiazem, digoxine, morphine, cyclosporins, buprenorphine, lidocaine, diazepam, nitrazepam, flurazepam, estazolam, flunitrazepam, triazolam, alprazolam, midazolam, temazepam, lormetazepam, brotizolam, clobazam, clonazepam, lorazepam, oxazepam, busiprone, sumatriptan, ergotamine

derivatives, cinnarizine, anti-histamines, ondansetron, tropisetron, granisetrone, metoclopramide, disulfiram, and vitamin K.

14. A composition as claimed in claim **11** wherein the tocopherol is α-tocopherol or an acetate, linoleate, nicotinate or hemi-succinate derivative thereof.

15. A composition as claimed in claim **11** in a form suitable for transmucosal, peroral, enteral or parenteral application.

16. A composition as claimed in claim **11**, in a form suitable for intranasal, buccal, vaginal or rectal application or for administration via the oral cavity.

17. A composition as claimed in claim **11**, wherein the active agent is a coronary drug selected from the group consisting of vasodilators; calcium-antagonists and cardiac-glycosides.

18. A composition as claimed in claim **11**, wherein the active agent is a benzodiazepine or an antimycotic.

19. A composition as claimed in claim **11**, wherein the active agent is selected from the group consisting of diazepam, midazolam and miconazole.

20. A composition as claimed in claim **11**, wherein the amount of the tocopherol or acetate, linoleate, nicotinate or hemi-succinate derivative thereof is from 35 to 80% (w/w).

21. A composition as claimed in claim **11**, further comprising at least one additional component selected from the group consisting of solvents, surfactants, stabilizers, bioadhesive polymers, preservatives, odor-masking agents and taste-masking agents.

22. A composition for the parenteral delivery of an active agent in the form of a non-liposomal emulsion comprising two phases:

a) a first tocopherol-based phase comprising an active agent which is no more than sparingly soluble in water and which is not a tocopherol; and

an amount of 20% to 95% w/w based on the total weight of the composition of at least one tocopherol or acetate, linoleate, nicotinate or hemi-succinate derivative thereof sufficient to dissolve the active agent in the tocopherol-based phase;

b) a second phase comprising an emulsifying agent wherein the emulsifying agent is vitamin E TPGS.

23. A composition as claimed in claim **22** wherein the active agent is selected from the group consisting of antibiotics; antivirals; antimycotics, anti-amoebics; non-steroidal anti-inflammatory drugs; anti-allergics; immunosuppressive agents; coronary drugs; analgesics, local anaesthetics; anxiolytics, sedative and hypnotics; migraine relieving agents; drugs against motion sickness; anti-emetics; disulfiram and vitamin K.

24. A composition as claimed in claim **23** wherein the active agent is selected from the group consisting of tetracycline, doxycycline, oxytetracycline, chloramphenicol, erythromycin, acyclovir, idoxuridine, tromantadine, miconazole, ketoconazole, fluconazole, itraconazole, econazole, griseofulvin, amphotericin B, nystatine, metronidazole, metronidazole benzoate, tinidazole, indomethacin, ibuprofen, piroxicam, diclofenac, Disodium cromoglycate, nitroglycerin, isosorbide dinitrate, verapamile, nifedipine, diltiazem, digoxine, morphine, cyclosporins, buprenorphine, lidocaine, diazepam, nitrazepam, flurazepam, estazolam, flunitrazepam, triazolam, alprazolam, midazolam, temazepam, lormetazepam, brotizolam, clobazam, clonazepam, lorazepam, oxazepam, busiprone, sumatriptan, ergotamine derivatives, cinnarizine, anti-histamines, ondansetron, tropisetron, granisetrone, metoclopramide, disulfiram, and vitamin K.

25. A composition as claimed in claim **22** wherein the tocopherol is α-tocopherol or an acetate, linoleate, nicotinate or hemi-succinate derivative thereof.

26. A composition as claimed in claim **22**, wherein the active agent is a coronary drug selected from the group consisting of vasodilators; calcium-antagonists and cardiac-glycosides.

27. A composition as claimed in claim **22**, wherein the active agent is a benzodiazepine or an antimycotic.

28. A composition as claimed in claim **22**, wherein the active agent is selected from the group consisting of diazepam, midazolam and miconazole.

29. A composition as claimed in claim **22**, wherein the amount of tocopherol or acetate, linoleate, nicotinate or hemi-succinate derivative thereof is from 35 to 80% (w/w).

30. A composition as claimed in claim **22**, further comprising at least one additional component selected from the group consisting of solvents, surfactants, stabilizers, bioadhesive polymers, preservatives, odor-masking agents and taste-masking agents.

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Clinical Commentary

Pharmacokinetics and tolerability of intranasal diazepam and midazolam in healthy adult volunteers

Ivaturi VD, Riss JR, Kriel RL, Cloyd JC. Pharmacokinetics and tolerability of intranasal diazepam and midazolam in healthy adult volunteers.
Acta Neurol Scand 2009: 120: 353–357.

Objective – The purpose of this pilot study was to determine the pharmacokinetics and tolerability of an investigational diazepam (DZP) formulation and a parenteral midazolam (MDZ) formulation following intranasal (i.n.) administration for the efficient treatment of seizure emergencies. *Methods* – Each subject received 5 mg of DZP and MDZ via both i.n. and intravenous routes in a four-way, randomized crossover trial. Blood samples were collected over 48 h. DZP and MDZ concentrations were measured using HPLC. Using analog scales, subjects rated tolerability (0 = no change from normal; 10 = maximum intolerability) and pain (0 = no pain; 4 = extreme pain) prior to and 0, 5, 15, 60 min, and 8 h after administration. *Results* – The C_{max} and T_{max} values for i.n. DZP and MDZ were 179.2 ng/ml and 28.8 min vs 62.8 ng/ml and 21.6 min, respectively. Immediately following i.n. administration, subjects reported tolerability scores of 6.75 and 6.0, and identical pain scores, 3.2, for DZP and MDZ, respectively. *Conclusion* – Both formulations were rapidly absorbed following i.n. administration with transient discomfort. DZP had a longer half-life, which may result in an extended duration of action. Further studies in large patient populations to evaluate the safety after long term use, efficacy and pharmacokinetics of i.n. DZP are warranted.

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Key words: diazepam; intranasal; midazolam; pharmacokinetics; tolerability

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Introduction

Individuals with uncontrolled epilepsy represent one of the greatest challenges in the management of this disorder (1, 2). These patients are particularly prone to status epilepticus (SE) as well as prolonged or cluster seizures which are in themselves serious conditions that can evolve into SE (3). Intravenously administered benzodiazepines (BZDs) are widely used for the treatment of seizure emergencies. When given within 30 min of seizure onset, intravenous (i.v.) BZDs are effective in more than 80% of patients (3, 4). However, i.v. administration requires skilled personnel and transport to a medical facility which can delay initiation of therapy (5). Treatment delay is associated with longer seizure duration, greater difficulty in terminating the seizure, prolonged hospitalization, higher mortality, and reduced quality of life (3, 6).

Administration of BZDs by other routes could permit earlier initiation of therapy outside of medical facilities. Rectal administration of diazepam (DZP) for the treatment of seizure emergencies is safe and effective, reduces medical costs, and improves quality of life, but many patients and their caretakers are reluctant to consider this mode of therapy especially when the patient is in a location which is socially embarrassing (7–10).

The availability of a fast-acting intranasal (i.n.) treatment that can be easily administered by the

patient or a caregiver would greatly improve the management of seizure disorders. Essential characteristics for an i.n. drug delivery system in the treatment of seizure emergencies include: patients must be able to tolerate the formulation; administration volume of 0.5 ml or less; rapid, consistent absorption; and easy administration by non-medical caregivers and patients.

The purpose of this study was to evaluate the pharmacokinetics and tolerability of i.n. administered DZP and midazolam (MDZ) in healthy adult volunteers.

Methods

The study was approved by the Institutional Review Boards at the University of Minnesota and Hennepin County Medical Center. Four healthy, non-pregnant women aged 20–24 years participated in the study. Subjects provided informed consent and were compensated for participation. Subjects were excluded if they were in poor health, unwilling or unable to receive i.n. or i.v. medications, pregnant, smokers, allergic to DZP or MDZ, or had narrow-angle glaucoma.

Subjects' treatment sequence was randomly assigned using a latin-square design. The study consisted of a four-way, randomized, single-blind, crossover design in which subjects received 5 mg doses of i.n. DZP, i.n. MDZ, i.v. DZP and i.v. MDZ. Subjects were admitted to the clinical research unit located at Hennepin County Medical Center and remained there for 8 h on four separate occasions after a minimum 1-week washout period.

Commercial formulations were used for i.v. administration of DZP and MDZ. The i.n. DZP formulation consisted of an investigational supersaturated solution containing 40 mg/ml of DZP, glycofurol and water. The injectable MDZ formulation (5mg/ml) was also used for i.n. administration. The i.n. doses of 5 mg were administered using a 1.0 ml syringe such that 0.125 ml of the DZP solution and 1 ml of the MDZ solution were dripped slowly into either one of the nostrils. Intranasal administration of normal saline (0.5 ml) given with a 1.0 ml dropper served as a control to compare tolerability of the drugs. Using a 10-point Global Tolerability Analog Scale, each subject rated overall tolerability of the i.n. (drug and normal saline) and i.v. doses (drug only) at 5 min prior to and 0, 5, 15, 60 min and 8 h after drug administration. A score of 10 was considered the least tolerable. This scale is analogous to Visual Analog Scales and has been adapted from a previous study evaluating the tolerability of a nasal formulation (11). Subjects also completed a pain and subjective discomfort questionnaire for the i.n. administrations. Using a 4 point analog scale with 4 representing extreme pain or discomfort, subjects rated specific pain characteristics: burning, stinging, and throbbing at −15, 0, 5, and 15 min.

Blood samples of 5 ml for pharmacokinetic analysis were collected, by means of a catheter inserted into a forearm vein, into glass tubes containing ethylenediamine tetraacetic acid as anticoagulant at −5, 0, 1, 5, 10, 20, 30, 60 min and 8 h. For DZP, additional samples were obtained at 24 and 48 h. Within 15 min of collection, the blood samples were spun in a centrifuge, and plasma was carefully separated. Plasma samples were stored at −80°C pending analysis.

Drug assay

Plasma samples were analyzed for MDZ and DZP concentrations using an Agilent 1100 series HPLC system (Agilent Technologies, Palo Alto, CA, USA) with a C4 column. The mobile phase for the system consisted of 40% acetonitrile and 60% phosphate buffer (pH-6.0). The flow rate of the mobile phase was 0.5 ml/min and the injection volume was 50 µl. Standard curves were prepared over the range of 5–500 ng/ml and quality control samples containing 15 (low), 50 (medium) and 250 ng/ml (high) of DZP and MDZ were prepared separately with blank human plasma.

An aliquot of 0.2 ml of the plasma was added to a 12 × 75 mm glass tube. A sample of NaOH (200 µl) and the internal standard lorazepam (200 µl) were added and the solution was mixed well. A 2 ml volume of ether was poured in the tube as an extracting solvent and vortex mixed for 1 min and then centrifuged for 10 min at 769 *g*. A sample of the organic layer was collected and evaporated until dry with nitrogen at 34°C, and then 200 µl of the HPLC mobile phase was added to dissolve the residue. After 30 s of vortex mixing, 50 µl of the sample solution was injected into the HPLC system.

The standards for DZP and MDZ were analyzed on separate days and the mean coefficients of variation were 5.6% and 5.0%, respectively. The mean coefficients of variation for the intraday variation of DZP and MDZ quality control samples were 8.6% and 7.5%, respectively.

Pharmacokinetic analysis

Concentration–time data of DZP and MDZ were examined using non-compartmental pharmacokinetics analysis with WinNonLin software (version 5.2; Pharsight Corporation, Mountain View, CA,

Table 1 Mean (±SD) pharmacokinetic parameters of diazepam (DZP) and midazolam (MDZ) in healthy volunteers following intravenous (i.v.) and intranasal (i.n.) administration of 5 mg dose

PK parameter	i.v. DZP	i.n. DZP	i.v. MDZ	i.n. MDZ
T_{max} (min)	–	28.8 ± 20.96	–	21.6 ± 7.63
C_{max} (ng/ml)	344.0 ± 92.81*	179.2 ± 8.85	165.2 ± 96.42*	62.8 ± 14.51
Half-life (h)	59.1 ± 7.76	22.4 ± 3.45	0.9 ± 0.60	3.0 ± 0.74

*Concentration 5 min after injection.

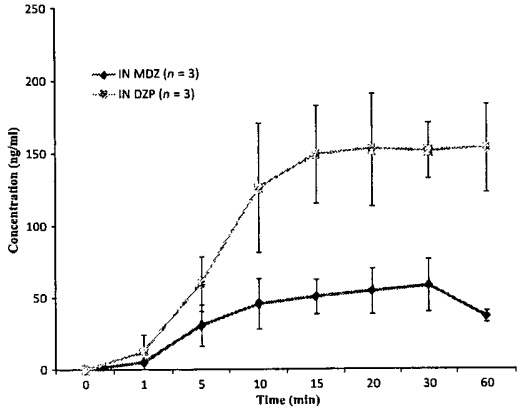

Figure 1. Comparison of mean intranasal diazepam and midazolam concentration vs time profile.

USA). The terminal rate constant (λz) was determined from the slope of the terminal log-linear portion of the plasma–concentration–time curve, and the terminal half-life ($t_{1/2}$) was calculated as $\ln 2/(\lambda z)$. Maximum plasma concentrations (C_{max}) and time to maximum concentration (T_{max}) were determined by direct observation of the data. Means and standard deviations for the parameters were also obtained using the descriptive statistics tool in WinNonlin version 5.2.

Results

Four women, aged 20–24 years entered the study. One subject dropped out due to travel conflicts after completing the i.n. DZP arm and was excluded from all group analyses. The pharmacokinetic parameters for the three subjects are summarized in Table 1. The mean concentration–time profiles are shown in Fig. 1 and the individual subject's concentration time profiles for both i.n. DZP and MDZ are shown in Fig. 2. The average i.n. DZP C_{max} and T_{max} were 179.2 ± 8.8 ng/ml and 28.8 ± 20.9 min, respectively. The average i.n. MDZ C_{max} and T_{max} were 62.8 ± 14.5 ng/ml and 21.6 ± 7.6 min, respectively. The C_{max} and T_{max} of the subject who dropped out of the study were 109.48 ng/ml and 20 min, respectively following i.n. DZP administration.

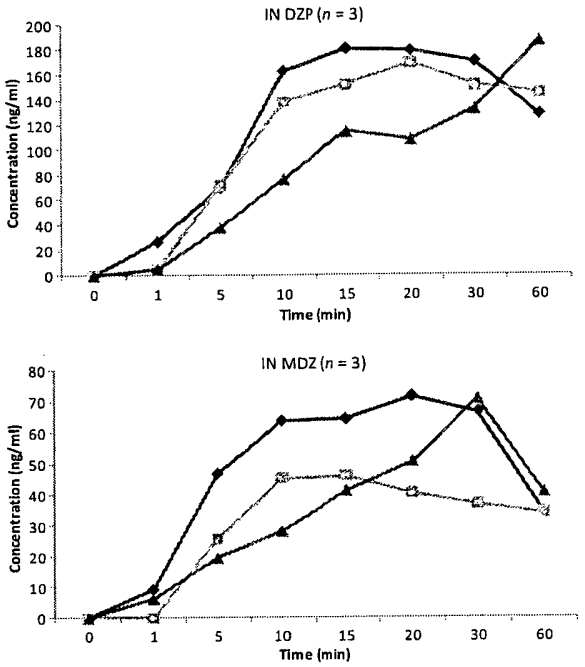

Figure 2. Concentration time profiles (0–60 min) of individual subjects (n = 3) for intranasal midazolam and diazepam.

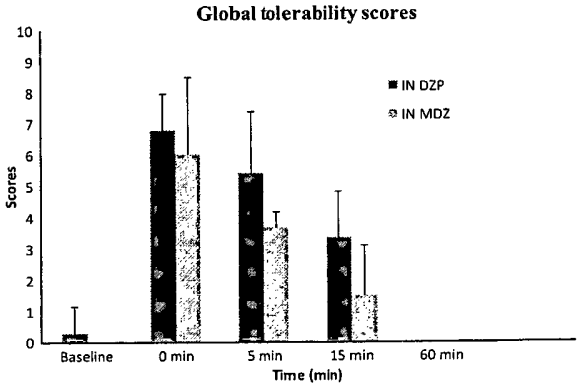

Figure 3. Comparison of mean global tolerability scores after intranasal administration (n = 3).

Immediately following i.n. administration, subjects reported an average global tolerability score of 6.75 and 6.0 for DZP and MDZ, respectively, which were statistically not different ($P > 0.05$) (Fig. 3). Within 15 min, scores decreased to 3.3 and 1.5, respectively, which eventually returned to baseline (Fig. 3).

Subjects rated both formulations as causing considerable pain with a maximum score of 3.2 immediately following nasal administration. Fifteen minutes later, the mean pain score for both drugs was 1.2. Posterior nasal drainage and watery eyes were reported by all subjects.

Discussion

Using PubMed with key terms 'intranasal midazolam and diazepam', we found no published reports directly comparing i.n. DZP and i.n. MDZ. Various MDZ formulations given i.n. have been investigated with most studies using the commercially available injectable MDZ solution (12, 13). These studies with doses between 10–20 mg (2–4 ml) reported C_{max} and T_{max} values in the range of 147–192 ng/ml and 14–25 min, respectively. The absorptive area of the nose limits the volume administered to approximately 0.1–0.3 ml per nostril although smaller volumes are preferable (14). When the commercially available injectable MDZ solution is given i.n., volumes exceeding 0.20 ml are required in order to administer a clinically relevant dose (12). This could affect both bioavailability and C_{max}. Highly concentrated investigational nasal MDZ formulations, including a water and propylene glycol admixture (pH 4) (15), and a solution containing 14% (w/v) sulfobutylether β-cyclodextrin (pH 4.3) (16) have also been studied in humans. Although these formulations permit administration of smaller volumes (0.2–0.3 ml), there was no distinguishable difference in the values of C_{max} and T_{max}.

Three previous studies have investigated i.n. DZP in humans. Gizurarson et al. compared an i.n. 2 mg dose of a 20 mg/ml DZP solution dissolved in 5% glycofurol in polyethylene glycol 200 with the same dose given i.v. (17). Blood samples were collected for 5 h following drug administration. The mean bioavailability was 50.4 ± 23.3% with a time to peak concentration of 18 ± 11 min. All subjects complained of nasal discomfort immediately following drug administration, but the discomfort resolved within 30 min. Lindhardt et al. evaluated an i.n. formulation of DZP in polyethylene glycol 300 in seven healthy volunteers. Using a crossover design, they compared 4 and 7 mg i.n. doses with a 5 mg i.v. dose and collected blood samples for 60 min after drug administration. The i.n. formulation had a relative bioavailability of 45% and 42%, a C_{max} of 99 and 179 ng/ml and a T_{max} of 18 and 42 min for the 4 and 7 mg doses, respectively (18). Given that the half-life of DZP ranges from 24 to 48 h, their bioavailability values are likely an underestimate of the actual extent of absorption. Lau and Slattery, using a 10 mg dose of DZP dissolved in Cremophor EL, reported a bioavailability of 78% with a C_{max} of 175 ng/ml and a T_{max} of 1 h (19). A recent study by Cloyd et al. (20) determined the pharmacokinetics and dose proportionality of 5 and 10 mg doses of an i.n. administered DZP formulation compared with i.v. administration in eight healthy volunteers using a crossover design. The formulation used was a 40 mg/ml supersaturated solution of DZP in glycofural–water cosolvent mixture. Each subject received two i.n. and one i.v. dose of DZP and blood samples were collected up to 48 h after dosing. The mean C_{max}, T_{max} and $t_{1/2}$ were 134.3 ±61.9 ng/ml, 55.6 ± 60.3 min, and 49.1 ± 20.4 h for the 5 mg dose, and 247.0 ± 60.9 ng/ml, 39.3 ± 38.1 min, and 57.0 ± 28.0 h for the 10 mg dose. Using analog scales, subjects rated tolerability (0 = no change from normal; 10 = maximum intolerability) prior to and 0, 5, 15, 60 min, and 8 h after administration. The mean tolerability scores observed were 4.4 and 4.7 for the 5 and 10 mg doses. Both these scores dropped down to 3 and 2.5, 15 min post-dose and to 1, 60 min post-dose.

The pharmacokinetic parameters for i.v. DZP and i.v. MDZ shown in Table 1 are comparable to those reported in the literature (21). The relationship between DZP pharmacokinetics and pharmacodynamics is complex. Following rapid i.v. administration, relatively high plasma DZP concentrations occur prior to distribution to various body compartments including the central nervous system (CNS). This makes correlation of DZP levels with seizure control difficult. In contrast, the absorption of DZP following rectal or nasal administration, although relatively rapid, does permit equilibration of DZP concentrations between plasma and the CNS. Milligan et al. rectally administered a 20 mg dose of DZP solution or placebo to 10 adults with epilepsy and then observed spike wave activity and measured plasma concentrations. Rectal DZP significantly reduced EEG spike frequencies within 20 min at a mean serum DZP level of 210 ng/ml. The mean C_{max} of DZP was 413 ng/ml and the mean T_{max} was 32 min (22). Based on these results, subsequent controlled clinical trials using similar doses, and presumably similar plasma DZP concentrations, have demonstrated that rectal DZP is effective in treating acute repetitive seizures (8).

Although we administered 5 mg DZP i.n. in this study, doubling the dose to 10 mg by giving 5 mg DZP into each nostril should result in concentrations >200 ng/ml that are attained within 5–10 min.

It is unclear whether prolonged serum DZP concentrations are needed to achieve and maintain seizure control. The longer elimination half-life of DZP compared with MDZ as shown in the results conveys a theoretical advantage in preventing subsequent seizure recurrence. In controlled investigations DZP is effective in treatment of seizure emergencies (8, 23). Such studies have yet to be conducted with MDZ.

All subjects reported moderate discomfort with both formulations. This is a major limitation of both the injectable MDZ solution and the investigational DZP formulation.

Measures to improve comfort level or tolerability are needed for greater patient acceptance. Nonetheless, some patients and caretakers would prefer the transient discomfort of the present i.n. formulations to rectal administration of medication in public settings. Similar views have been expressed in a comparative study of i.n. MDZ and rectal DZP (10). Intranasal DZP may be useful in the treatment of seizure emergencies. However, this was a small study of healthy volunteers which precludes generalization to clinical use and further research is needed to improve tolerability of the formulation and to characterize the appropriate dose.

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AMENDED CLAIMS

1. A pharmaceutical solution for use in a method of treating seizures by nasal administration of said pharmaceutical solution which consists of:

(a) a benzodiazepine drug;

(b) one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from 30% to 95% (w/w);

(c) 1-25% (w/v) ethanol and 1-25% (w/v) benzyl alcohol, in a combined amount from 10% to 50% (w/w); and

(d) an alkyl glycoside.

2. The use of the pharmaceutical solution of claim 1 in treating seizures, wherein the benzodiazepine drug is selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, any pharmaceutically-acceptable salts thereof, and any combinations thereof.

3. The use of the pharmaceutical solution of claim 2 in treating seizures, wherein the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof.

4. The use of the pharmaceutical solution of claim 1 in treating seizures, containing 1 to 20% (w/v) of benzodiazepine.

5. The use of the pharmaceutical solution of claim 4 in treating seizures, containing 1 to 20% (w/v) of diazepam.

6. The use of the pharmaceutical solution of claim 1 in treating seizures, wherein the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ- tocotrienol, δ- tocotrienol, tocophersolan, any isomers thereof, any esters thereof, any analogs thereof, and any combinations thereof.

7. The use of the pharmaceutical solution of claim 1 in treating seizures, containing 10-22.5% (w/v) ethanol and 7.5-12.5% (w/v) benzyl alcohol.

8. The use of the pharmaceutical solution of claim 1 in treating seizures, wherein the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from 45% to 85% (w/w).

9. The use of the pharmaceutical solution of claim 1 in treating seizures, consisting of 5-15% (w/v) diazepam, 0.01-1% (w/v) alkyl glycoside, 45-65% (w/v) vitamin E, 10-25% (w/v) ethanol and 5-15% (w/v) benzyl alcohol.

10. The use of the pharmaceutical solution of claim 1 in treating seizures, wherein the pharmaceutically-acceptable formulation comprises at least 0.01% (w/w) of an alkyl glycoside.

11. The use of the pharmaceutical solution of claim 10 in treating seizures, wherein the pharmaceutically-acceptable formulation 0.01% to 1% (w/w) of dodecyl maltoside.

12. The use of the pharmaceutical solution of claim 1 in treating seizures, consisting of diazepam, vitamin E, ethanol, benzyl alcohol, and dodecyl maltoside.

13. The use of the pharmaceutical solution of claim 1 in treating seizures, consisting of 5-15% (w/v) diazepam, 45-65% (w/v) vitamin E, 10-25% (w/v) ethanol, 5-15% (w/v) benzyl alcohol, and 0.01%-1% (w/v) dodecyl maltoside.

14. The use of the pharmaceutical solution of claim 1 in treating seizures, consisting of 10% (w/v) diazepam, 56.47% (w/v) vitamin E, q.s. dehydrated ethanol, 10.5% (w/v) benzyl alcohol, and 0.25% (w/v) dodecyl maltoside.

AMENDED CLAIMS

1. A pharmaceutical solution for use in a method of treating seizures by nasal administration of said pharmaceutical solution which consist~~ings~~ of:

(a) a benzodiazepine drug;

(b) one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from 30% to 95% (w/w);

(c) 1-25% (w/v) ethanol and 1-25% (w/v) benzyl alcohol, in a combined amount from 10% to ~~7~~50% (w/w); and

(d) an alkyl glycoside~~,~~

~~for use in treating seizures~~.

2. The use of the pharmaceutical solution of claim 1 in treating seizures, wherein the benzodiazepine drug is selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, any pharmaceutically-acceptable salts thereof, and any combinations thereof.

3. The use of the pharmaceutical solution of claim 2 in treating seizures, wherein the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof.

4. The use of the pharmaceutical solution of claim 1 in treating seizures, containing 1 to 20% (w/v) of benzodiazepine.

5. The use of the pharmaceutical solution of claim 4 in treating seizures, containing 1 to 20% (w/v) of diazepam.

6. The use of the pharmaceutical solution of claim 1 in treating seizures, wherein the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-

tocotrienol, γ- tocotrienol, δ- tocotrienol, tocophersolan, any isomers thereof, any esters thereof, any analogs thereof, and any combinations thereof.

~~7. The use of the pharmaceutical solution of claim 1 in treating seizures, containing 1-25% (w/v) ethanol and 1-25 % (w/v) benzyl alcohol.~~

~~8~~7. The use of the pharmaceutical solution of claim 1 in treating seizures, containing 10-22.5% (w/v) ethanol and 7.5-12.5% (w/v) benzyl alcohol.

~~9~~8. The use of the pharmaceutical solution of claim 1 in treating seizures, wherein the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from 45% to 85% (w/w).

~~10~~9. The use of the pharmaceutical solution of claim 1 in treating seizures, consisting of 5-15% (w/v) diazepam, 0.01-1% (w/v) alkyl glycoside, 45-65% (w/v) vitamin E, 10-25% (w/v) ethanol and 5-15% (w/v) benzyl alcohol.

~~11~~10. The use of the pharmaceutical solution of claim 1 in treating seizures, wherein the pharmaceutically-acceptable formulation comprises at least 0.01% (w/w) of an alkyl glycoside.

~~12~~11. The use of the pharmaceutical solution of claim ~~11~~ 10 in treating seizures, wherein the pharmaceutically-acceptable formulation 0.01% to 1% (w/w) of dodecyl maltoside.

~~13~~12. The use of the pharmaceutical solution of claim 1 in treating seizures, consisting of diazepam, vitamin E, ethanol, benzyl alcohol, and dodecyl maltoside.

~~14~~13. The use of the pharmaceutical solution of claim 1 in treating seizures, consisting of 5-15% (w/v) diazepam, 45-65% (w/v) vitamin E, 10-25% (w/v) ethanol, 5-15% (w/v) benzyl alcohol, and 0.01%-1% (w/v) dodecyl maltoside.

~~15~~14. The use of the pharmaceutical solution of claim 1 in treating seizures, consisting of 10% (w/v) diazepam, 56.47% (w/v) vitamin E, q.s. dehydrated ethanol, 10.5% (w/v) benzyl alcohol, and 0.25% (w/v) dodecyl maltoside.

(marked up version)

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Wichmann, Hendrik
Wuesthoff & Wuesthoff
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81541 München
ALLEMAGNE

Date
16.05.2017

Reference	Application No./Patent No.
EPA-124 519	12801372.9 - 1455 / 2720699

Applicant/Proprietor
Hale BioPharma Ventures, LLC

Summons to attend oral proceedings pursuant to Rule 115(1) EPC

You are hereby summoned to attend oral proceedings arranged in connection with the above-mentioned European patent application.

The matters to be discussed are set out in the communication accompanying this summons (EPO Form 2906).

The oral proceedings, which will not be public, will take place before the Examining Division

on 01.12.17 at 09.00 hrs as a video-conference

No changes to the date of the oral proceedings can be made, except on serious grounds (see OJ EPO 1/2009, 68). If you do not appear as summoned, the oral proceedings may continue without you (R. 115(2) EPC, see also OJ EPO 10/2008, 471).

Your attention is drawn to Rule 4 EPC, regarding the language of the oral proceedings, and to the Special edition No. 3 OJ EPO 2007, L.1., concerning the filing of authorisations for company employees and lawyers acting as representatives before the EPO.

The final date for making written submissions and/or amendments (R. 116 EPC) is 01.11.17.

During the video-conference the examining division will be located in Room S1.18 at the EPO in Rijswijk (NL).

In this respect, you are informed that the EPO video-conference studios employ IP technology (SIP or H.323, Videocoding CIF H.261, H.263, H.264, Audiocoding G.711, G.722, max. transmission rate 1024 Kbit/s). Your video-conference equipment should meet a minimum transmission rate of at least 256 Kbit/s, but at least 384 Kbit/s is preferred.

Concerning establishing the required video-conference link you are further informed of the following:

- conference room video IP address:	69079357@cvc.epo.org
- conference room telefax number:	(0031) 70 340 9412
- conference room telephone number:	(0031) 70 340 9357
- telephone number in case of connection difficulties:	(0031) 70 340 4444

The applicant or representative is encouraged to set up a connection to a demonstration system well before the oral proceedings take place. For this purpose please connect to the demo system under "demo01@cvc.epo.org" at any time.

Please supply the EPO as soon as possible with the following information concerning your videoconference studio:

- type and name of VICO equipment
- telephone and fax number of the studio including country and area code
- dialling number to reach the studio including country and area code
- transmission speed in Kbit/s
- name of contact person with telephone number and email address

1st Examiner:
Gómez Gallardo S

2nd Examiner:
Ceyte M

Chairman:
Lamers W

For the Examining Division

Annexes:
Confirmation of receipt (Form 2936)
Communication (EPO Form 2906)

Europäisches Patentamt
European Patent Office
Office européen des brevets

European Patent Office
Postbus 5818
2280 HV Rijswijk
NETHERLANDS
Tel: +31 70 340 2040
Fax: +31 70 340 3016

Application No.: 12 801 372.9

Preparation for oral proceedings - Instructions to Support Service

Oral proceedings are to be held in connection with the above patent application

1. The matters to be discussed are set out in the annex (Form 2906)

2. Dispatch the summons using Form 2008/2310 and Form 2906 for the parties to attend on:

Day 01.12.2017 Time 09:00

Archibus

Oral proceedings to be held by Videoconference

Conference Room S1.18 booked

ORAL 01, 02, 03 and 05 coded

11-05-2017 W. HÜBNER

Date Initials

2.1 Parties' submissions in preparation for the oral proceedings, if any, should be made no later than

1 month(s)

before the date of the oral proceedings (transfer to Form 2008.1 / 2310.1)

2.2 Encode ORAL(04)

coded

11-05-2017 W. HÜBNER

Date Initials

2.3 Dispatch Form 2008.7 / 2310.7 to division

11-05-2017 W. HÜBNER

Date Initials

3. ☐ Arrange for the following special equipment to be provided in the conference room:

Date Initials

Europäisches Patentamt
European Patent Office
Office européen des brevets

European Patent Office
Postbus 5818
2280 HV Rijswijk
NETHERLANDS
Tel: +31 70 340 2040
Fax: +31 70 340 3016

4. Return the dossier to primary examiner with Form 2041
(15 days before the oral proceedings)

....
Date Initials

26/4/2017
Date

Lamers, Wolfram Chairman	Ceyte, Mathilde 2nd examiner	Gómez Gallardo, S 1st examiner	Legal member

Enclosure(s):

The examination is being carried out on the **following application documents**

Description, Pages

1-65 as published

Claims, Numbers

1-14 received on 12-01-2017 with letter of 12-01-2017

Drawings, Sheets

1/5-5/5 as published

1. As requested by the applicant, the examining division herewith appoints Oral Proceedings, in accordance with Art. 116 EPC. The following issues will be discussed in the course of the Proceedings:

-Inventive step (Art. 56 EPC),

-Methods of treatment (Art. 53(c) EPC) and

-Clarity (Art. 84 EPC)

2. CITED DOCUMENT

Reference is made to the following document; the numbering will be adhered to in the rest of the procedure.

D6 US 2009/258865 A1 (HALE BIOPHARMA VENTURES LLC [US]) 15 October 2009 (2009-10-15); cited in the International Search Report

3. INVENTIVE STEP (Art. 56 EPC)

3.1. Claim 1 has been limited to the specific amounts of ethanol and benzyl alcohol. Therefore, novelty is acknowledged vis-à-vis D6.

3.2. Document D6 is considered to be the closest prior art to the subject-matter of claim 1. This document discloses (cf. paragraphs 34 and 36) an intranasal solution consisting of (a) a benzodiazepine drug (preferably diazepam), (b) one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount of 30-95% (w/w), and (c) one or more alcohols or glycols, or any combinations thereof, in an amount of 10-70% (w/w). The one or more alcohols are selected from the group consisting of ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, or any combinations thereof (cf. paragraph 39). The solution is also disclosed to comprise one or more alkyl glycosides (cf. paragraphs 45-47), and to be used for the treatment of seizures (cf. paragraphs 78, 82-84, 88-90, 94-96, 100-102, 106-108, 112-114, 119-121, 125-127 and 131, and examples 1, 2, 9 and 10).

The subject-matter of claim 1 differs from D6 in:

-the selection of a specific mixture of ethanol and benzyl alcohol as the alcohols of the solution,

-the selection of an amount of 1-25% (w/v) of ethanol and 1-25% (w/v) of benzyl alcohol and

-the selection of 10-50% (w/w) as the total amount of ethanol and benzyl alcohol.

Arguments of the applicant

To explain the effect of the above distinguishing features, the applicant referred in his letter of 21.10.2015 to the bioavailability study of Table 11-3 performed with (a) the solution of the application comprising diazepam, alpha-tocopherol, ethanol, benzyl alcohol and dodecyl maltoside (Table 11-1), and (b) a suspension of the prior art, said suspension comprising diazepam, vitamin E TPGS, propylene glycol, povidone, methyl paraben, propyl paraben, dodecyl maltoside and water (Table 11-2). According to this study, the solution of the application yields a greater total drug exposure over time compared to the prior art suspension. A post-published article, namely *Agarwal et al, Epilepsy Research (2013), 105, 362-367*, was filed in support of the above and also to show that the nasal solution of claim 1 is well tolerated without serious adverse effects. According to the letter of the applicant of 12.01.2017, the above would demonstrate that the solution with which the application is concerned has a high degree of bioavailability and is generally well-tolerated. With the same letter, the applicant additionally filed the article *Ivatury et al, Acta Neurol Scand*

(2009), 120, 353-357. This article teaches that a supersaturated intranasal solution containing 40 mg/ml of diazepam, glycofurol and water is irritating. This would show, according to the applicant, that the prior art compositions are irritating whereas the composition of claim 1 is not.

In view of the above, the applicant submitted that the problem underlying claim 1 would be the provision of an improved intranasal solution. Since it cannot be derived from the prior art that the combination of ethanol and benzyl alcohol provides a superior drug exposure and, furthermore, is not irritating, an inventive step should be acknowledged for claim 1.

In the event that the examining division would not acknowledge an improvement, the problem could be reformulated in a less ambitious way as the provision of an intranasal solution as an alternative to the prior art solutions and which is also tolerable (cf. *Agarwal et al, Epilepsy Research (2013), 105, 362-367*). At this point, the applicant referred to document US 6,193,985 B1, concerned with the use of tocopherol as a solvent and/or emulsifier in the preparation of compositions to be administered to mucosal membranes, preferably by nasal, rectal and oral routes. The passage in column 3, lines 65-67 was specifically referred to, reading that the viscosity of these compositions can be reduced by adding co-solvents such as ethanol, although this is less desired because the solutions of this kind tend to be irritating to certain mucosal tissues. The applicant also pointed out that the benzodiazepine compositions of the examples, either in the form of emulsions or in the form of solutions, do not comprise any alcohols or glycols nor any alkylglycosides. They are instead formulated with oils. According to the applicant, the document US 6,193,985 B1 would, therefore, teach away from the use of ethanol to formulate benzodiazepine compositions. In other words, there was no reasonable expectation of success that the claimed combination of ethanol and benzyl alcohol can provide tolerable intranasal solutions, so an inventive step should be acknowledged for claim 1.

Counter-arguments of the examining division

The division has the following remarks with respect to the above argumentation of the applicant:

-The suspension of the prior art of Table 11-2 not only differs from the solution of claim 1 in the solvent that has been used (propylene glycol + water versus ethanol + benzyl alcohol) but also in the incorporation in the formulation of povidone, methyl paraben, and propyl paraben. This means that the above prior art suspension is not suitable for comparison purposes, as in said suspension more than one variable has been changed, and, therefore, it is unclear whether the poorer bioavailability is due to the formulation being a suspension instead of a solution, to the suspension containing povidone, to the suspension containing the two parabens, or to the suspension containing propylene glycol + water instead of ethanol + benzyl alcohol. Any comparison between these two formulations is, thus, not conclusive for the assessment of inventive step.

-In *Agarwal et al, Epilepsy Research (2013), 105, 362-367*, it is concluded that both the solution of claim 1 and the suspension of Table 11-2 are well tolerated. Thus, the tolerability effect does not result from the combination of ethanol + benzyl alcohol.

-The attention of the applicant is drawn to the fact that any unexpected effect of the composition of the application should be demonstrated with respect to the composition of the closest prior art. In other words, the applicant should demonstrate that the use of a combination of ethanol + benzyl alcohol provides a surprising advantage compared to any other alcohol or combination of alcohols disclosed in D6 (i.e. ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, or any combinations thereof). There should, therefore, be an improvement not when compared with any prior art compositions but when compared with the composition of the closest prior art. In view of this, the fact that the formulation of *Ivatury et al, Acta Neurol Scand (2009), 120, 353-357*, namely, a supersaturated intranasal solution containing 40 mg/ml of diazepam, glycofurol and water, is irritating cannot support the presence of an inventive step because glycofurol is not listed as one of the possible alcohols of the closest prior art D6.

-With respect to the vague statement of US 6,193,985 B1 that the viscosity of compositions intended for a variety of mucosal tissues can be reduced by adding co-solvents such as ethanol, although this is less desired because the solutions of this kind tend to be irritating to certain mucosal tissues: this statement does not imply that ethanol is the only irritating co-solvent; in other words, other co-solvents, also listed in D6, are not excluded which could also be irritating to mucosal tissues; in addition, there is no direct link in US 6,193,985 B1 between ethanol and the irritation of the

nasal mucosa. It is noted that, starting from D6, any combination of alcohols including ethanol, propyl alcohol, butyl alcohol, pentanol and benzyl alcohol is possible and, furthermore, in paragraph 39, ethanol is disclosed as one of the preferred alcohols to be used.

Since the arguments of the applicant as well as the data provided so far are not conclusive as to the presence of an unexpected effect with respect to the closest prior art, the objective technical problem underlying claim 1 has to be regarded as the provision of an alternative intranasal solution for treating seizures.

It is established Case Law that, when the technical problem is simply that of providing a further composition of matter, *i.e.* simply that of providing an alternative to the prior art, any feature (or combination of features) already conventional for that sort of composition of matter represents an equally suggested or obvious solution to the posed problem. Thus arbitrarily selecting one among equally obvious alternative variations is deprived of any inventive character. Even if the skilled person "could" also have taken into consideration other conventional modifications of the prior art, the existence of such other obvious solutions does not render inventive the one leading to claims directed to such alternative subject-matter. The skilled person thus "would do what he could", and would combine ethanol with benzyl alcohol based on the list of alcohols and combinations thereof disclosed in D6. Furthermore, paragraph 42 discloses further possible ranges and absolute values for the combined amount of the one or more alcohols or glycols. The value of 50% (w/w) is one of those listed. Therefore, the range 10-50% (w/w) for the combined amount of the one or more alcohols or glycols is unambiguously derivable from D6. In the absence of any evidence of an unexpected effect associated therewith, the person skilled in the art would consider adjusting the amounts of ethanol and benzyl alcohol by mere routine experimentation so that the total amount is 10-50% (w/w). By doing so, he or she would inevitably arrive at the amounts 1-25% (w/v) and 1-25% (w/v) of claim 1, without exercising any inventive skill.

No inventive step can, therefore, be acknowledged for claim 1.

3.3. The further features of dependent claim 2-14 are either disclosed in D6 or, in the absence of any surprising advantage related thereto, represent obvious modifications for the skilled person. Therefore, these claims are not inventive either.

3.4. An inventive step could be acknowledged for claim 1 if it would be demonstrated that an unexpected technical effect is associated to the specific combination of ethanol and benzyl alcohol at the claimed amounts that does not exist when using the other alcohols listed in D6. Any reference to other prior art compositions comprising other solvents, not listed in D6, will not be considered to be relevant for the analysis of inventive step.

4. METHODS OF TREATMENT (Art. 53(c) EPC) and CLARITY (Art. 84 EPC)

Dependent claims 2-14 introduce a problem of lack of consistency because they refer to the "use of the pharmaceutical solution of claim... in treating seizures" while claim 1 refers to "a pharmaceutical solution for use in a method of treating seizures...". Furthermore, the wording "use of the pharmaceutical solution of claim... in treating seizures" is directed to a method of treatment, which is excluded from patentability under Art. 53(c) EPC. Claims 2-14 should be reworded to read "the pharmaceutical solution for use according to..." to be consistent with claim 1 and to be in line with Art. 54(4) and (5) EPC.

5. CLARITY (Art. 84 EPC)

In claim 11, the term "comprises" is missing after the term "formulation".

6. CONCLUSIONS

6.1. The division noted the request of the applicant with letter of 12.01.2017 that the Proceedings are held by video-conference.

6.2. The division draws the attention of the applicant to the notice from the European Patent Office concerning non-attendance at Oral Proceedings published in the Official Journal 10/2008, page 471. In this information, it is mentioned that if the applicant decides not to attend the Proceedings, he has to expect that a decision based on the objections which arise against the amended claims could be taken during the Proceedings in his absence. The applicant is also reminded of the possibility of requesting a "decision according to the state of the file", which can be appealed (cf. Guidelines, C-V, 15). It should be noted that such a request can only be followed by the division if no further comments or amendments are submitted by the applicant in response to these summons, and the request for oral proceedings is withdrawn.

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GERMANY

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Wichmann, Hendrik
Wuesthoff & Wuesthoff
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Schweigerstraße 2
81541 München
ALLEMAGNE

Date: 16.05.2017

Reference	Application No./Patent No.
EPA-124 519	12801372.9 - 1455 / 2720699

Applicant/Proprietor: Hale BioPharma Ventures, LLC

EPA/EPO/OEB Formblatt/Form/Formulaire : F2008

Empfangsbescheinigung über den Zugang des vorstehend bezeichneten Schriftstücks
Acknowledgement of receipt of the document specified above
Récépissé du document spécifié ci-dessus

Unter Bezugnahme auf die Mitteilung im ABl EPA 7/2010, 377 wird gebeten, die Empfangsbescheinigung mit Empfangsdatum und Unterschrift zu versehen und **umgehend** an das EPA zurückzusenden:

With reference to the Notice in OJ EPO 7/2010, 377, you are requested to date and sign the acknowledgement of receipt and return it to the EPO **immediately**:

Conformément au communiqué paru au JO OEB 7/2010, 377, vous êtes prié d'indiquer sur le récépissé la date de réception du document, de signer le récépissé et de le renvoyer **sans délai** à l' OEB:

- **über die Online-Dienste des EPA** (als Anlage zu EPA Form 1038) / **through EPO Online Services** (as annex to EPO Form 1038) / **par les services en ligne de l'OEB** (en tant que pièce jointe au formulaire OEB 1038),
- **per Fax / by fax / par téléfax (+49 (0) 89 2399-4465 or +31 (0) 70 340-3016)**
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29. Mai 2017

Date
16.05.2017

Reference	Application No./Patent No.
EPA-124 519	12801372.9 - 1455 / 2720699

Applicant/Proprietor
Hale BioPharma Ventures, LLC

EPA/EPO/OEB Formblatt/Form/Formulaire : F2008

Empfangsbescheinigung über den Zugang des vorstehend bezeichneten Schriftstücks
Acknowledgement of receipt of the document specified above
Récépissé du document spécifié ci-dessus

Unter Bezugnahme auf die Mitteilung im ABl EPA 7/2010, 377 wird gebeten, die Empfangsbescheinigung mit Empfangsdatum und Unterschrift zu versehen und **umgehend** an das EPA zurückzusenden:

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Conformément au communiqué paru au JO OEB 7/2010, 377, vous êtes prié d'indiquer sur le récépissé la date de réception du document, de signer le récépissé et de le renvoyer **sans délai** à l' OEB:

- **über die Online-Dienste des EPA** (als Anlage zu EPA Form 1038) / **through EPO Online Services** (as annex to EPO Form 1038) / **par les services en ligne de l'OEB** (en tant que pièce jointe au formulaire OEB 1038),
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Op kantoor van verzending in te vullen / To complete at office of posting

Kantoor van verzending Office of posting	**Datum** Date 16.05.2017

Geadresseerde van de zending
Addressee of the item

Wichmann, Hendrik
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Patentanwälte PartG mbB
Schweigerstraße 2
81541 München
GERMANY

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Naam, datum en handtekening
Name, date and signature
Christiane Chauvet
26/05/17

* Afhankelijk van de voorschriften in het land van bestemming wordt het bericht getekend door de geadresseerde of zijn gemachtigde of door de postmedewerker 26.5.17

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RD 122 144 185 NL - 16-05-2017 - 12801372.9 - 1455-WI

P 2162 (versie 0708) - CP7808 TNT Post BV, Handelsregister K.v.K. Haaglanden nr. 27124700

APPLICANT'S EXHIBIT 1040

WUESTHOFF & WUESTHOFF

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URGENT

Please directly deliver to the Primary Examiner

2 November 2017

European Patent Application 12 801 372.9-1455
based on PCT/US2012/042311
Applicant: Hale BioPharma Ventures, LLC
Our ref.: EPA-124 519

In response to the Summons pursuant to Rule 115(1) EPC dated 16 May 2017

The Applicant hereby provides written submissions in preparation for Oral Proceedings before the Examining Division, currently arranged for 1 December 2017. These submissions consist of arguments and explanations as set out in this document, a Main Request and a First and Second Auxiliary Request. Marked up copies of the requests are provided showing the changes made to generate each request from the claims previously on file.

It is earnestly believed that on the basis of the following submissions the Main Request relates to patentable subject matter. The Auxiliary Requests are, of course, put forward as alternatives and more restricted claims. The arguments advanced for the Main Request also apply to the Auxiliary Requests, but have not been duplicated for the sake of brevity.

I Formalities

Applicant will be represented at the Oral Proceedings by the undersigned. We will use English language.

The information about our videoconference studio are as follows:

1) Type and name of VICO equipment: Aver EVC300;
2) telephone number including country and area code: +49 89 621 800 860;
3) fax number including country and area code: +49 89 621 800 882;
4) dialling number to the studio incl. country and area code: +49 89 621 800 860;
5) transmission speed in Kbit/s: 1024 Kbit/s Up (> 10 Mbit/s Down);
6) contact person: Mr. Christoph Scheich (IT administrator), +49 89 621 800 0, wuesthoff@wuesthoff.de;
7) technology VICO: IP.

II Requests

1 The Applicant respectfully requests the Examining Division to review the submissions and to contact the undersigned if they do not agree with the Main Request. Applicant believes that all the requests filed herewith represent allowable subject matter.

2 Thus, it is requested to grant a European patent based on the set of claims of the Main Request as well as the amended specification pages submitted herewith (which replace the specification as on file) and the original figures. Should the Main Request not be considered allowable, it is requested to grant a patent on the basis of the claims of the Auxiliary Request 1 or 2 (in this order).

III Main Request

1 Amendments and Support

The claims have been reworded to comply with the current second medical use claim format. In addition, the clarity objection against former claim 11 has been addressed. Finally, the additional presence of APIs and excipients has been defined in claim 1 based on paragraph [019] and [020] of the original application. The remaining amendments are of formal nature only and are indicated in the markup version.

Support for the subject matter of the claims of the request may be found at least at:

Claim	Basis in PCT/US2012/042311 as filed
1	[010], [011], [072], [083], [084], original claims 1, 8, 10, 33 as well as [019] and [020]
2	[010], [011], [022], [079], [085]-[0133], [0173], original claim
3	[010], [011], original claim 5, 28
4	[010], [011], original claim 6, 29
5	[010], [011], [014], [023], [044], [058], [0138], Original claim
6	[010], original claim 11
7	[017], [026], [047], [061], original claim 13, 36
8	[010], [011], original claim 17, 56, 57, 60
9	[010], original claim 18, 19, 49, 50
10	[010], [011], original claim 19, 22, 51, 54, 56, 57-62
11	Original claim 21, 22, 23, 52, 53, 57, 58,
12	[010], [011], original claim 22, 54, 56, 57, 60
13	Original claim 22, 54

2 Novelty

In the Communication dated 16 May 2017, the previous claims were considered novel vis-à-vis US 2009/258865 (Communication at 3.1).

3 Inventive Step

3.1 The comparative data are meaningful and show the effects as provided by the features distinguishing over D6

The Examining Division sets forth that D6 discloses a number of alcohols, including ethanol, propyl alcohol, butyl alcohol, pentanol and benzyl alcohol and that D6 discloses that the alcohol or combinations of alcohols may comprise about 50% (w/w) of the carrier system (Communication of 16 May 2017, 3.2).

Further, the Examining Division formulates the objective technical problem to be solved as an alternative intranasal solution for treating seizures, which leads to a conclusion of obviousness (Communication of 16 May 2017, 3.2).

In contrast, the Applicant will show that the objective technical problem to be solved is providing an intranasal formulation for treating seizures, the intranasal formulation having increased bioavailability. Applicant believes that under such a framework, the claims possess an inventive step over the prior art.

According to the Examining Division, the comparison of the suspension of Table 11-2 with the solution of Table 11-1 of the application would not be meaningful, because the suspension of Table 11-2 not only differs from the solution of claim 1 in the solvent but also in the incorporation of povidone, methyl paraben and propyl paraben. The person of skill in the art would appreciate that both formulations contain diazepam, vitamin E, methylparaben, propylparaben, propylene glycol, povidone, and water.

Applicant strongly disagrees with the conclusion that the comparison is not meaningful.

According to established case law of the Boards of Appeal, it has to be convincingly shown that the alleged effect has its origin in the distinguishing feature (see Case Law of the Boards of Appeal of the EPO; 7th Edition, 2013, page 178, 4th paragraph; in particular **T 197/86**, OJ 1989, 371, **T 1835/07**).

As acknowledged by the Examining Division, claim 1 differs over D6 by the selection of the specific solvent mixture, i.e. ethanol and benzyl alcohol.

In addition, D6 equally discloses both solutions (see e.g., [0034]) and suspensions (see e.g., [0038]) of benzodiazepine, while claim 1 of the present application only refers to solutions. Accordingly, claim 1 of the present application is based on the selection of solutions over suspensions.

Accordingly, if it can be convincingly demonstrated that a solution on the basis of ethanol + benzyl alcohol provides an improvement over a suspension containing glycol + water as in D6, it is not relevant whether the improvement is caused by the feature "suspension" or "ethanol + benzyl alcohol", since both features represent distinguishing over D6.

Furthermore, propylene glycol, povidone, and water combine to form a suspension, wherein Table 11-2 indicates povidone as the suspending agent. Beyond that, there is no technical rational that povidone influences bioavailability. As such, the presence of povidone can be no additional "cause" for the claimed improvement. Rather, the distinguishing feature "solution" version "suspension" covers the use of such suspending agents and any improvement of the solution over a suspension with povidone as suspending agent, hence, contributes to an inventive step.

In view of the above, it only has to be assessed, whether the demonstrated improvement has its origin in the following differences between the suspension/solution of Table 11-2/11-1 of the application:

- "Suspension or solution" (caused by the presence of e.g., povidone in the suspension of Table 11-2) and "ethanol+benzyl alcohol or glycol+water" or
- Presence of methyl parabene and propyl parabene in the suspension of Table 11-2.

Parabens are well-known to be preserving agents, and thus do not contribute to a formulation's bioavailability. The presence of methylparaben and propylparaben is therefore not relevant when discussing bioavailability of a formulation. Accordingly, it is credible that the claimed improvement is **not** caused by the absence of methyl parabene and propyl parabene in the solution of Table 11-1.

With respect to the claimed benefits, Applicant points to Table 11-3 of the instant specification, which compares bioavailability parameters between the instantly claimed benzodiazepine solution and the closest-prior-art diazepam suspension of Table 11-2. As will be explained in more detail in Section 3.2, as both the instant claims and the closest-prior art diazepam formulation contain an alkyl glycoside, Figures 1-3 demonstrate the superior bioavailability of the claimed co-solvent system of ethanol and benzyl alcohol over the closest prior art. Thus, while Intravail A3 increases the bioavailability of a formulation, the co-solvent system of 1-25% ethanol and 1-25% benzyl alcohol provides an unexpected increase in bioavailability over and above the increase in bioavailability from Intravail A3.

It is therefore requested to acknowledge that the claimed combination of features provides an improvement over the prior art.

The *objective technical problem* underlying the amended claims can therefore be formulated as providing an improved pharmaceutical solution for use in a method of treating seizures by nasal administration of said pharmaceutical solution, wherein the bioavailability of said pharmaceutical solution is higher.

Since there is no teaching in the cited prior art regarding how to solve the technical problem of providing an improved intranasal solution, the claimed subject-matter was not obvious.

Notably, D6 does not contain any bioavailability data; therefore the skilled artisan could not find the solution to the technical problem within the cited reference D6.

Furthermore, there is no *direct and unambiguous* mention of this particular combination in individualized form in D6, let alone in the claimed amounts.

Rather, paragraph [0039] of D6 encompasses the use of

- only one alcohol,

- the use of ethanol in combination with alcohols other than benzyl alcohol,

- the use benzyl alcohol in combination with alcohols other than ethanol, and

- combinations without ethanol or benzyl alcohol (e.g., propyl alcohol + butyl alcohol).

Already in view of the above, it is submitted that the claimed subject-matter is based on an inventive step.

3.2 A comparison of the suspension/solution of Table 11-2/11-1 of the application represents a proper comparison over the closest prior art

Applicant disagrees with the Examining Division that the unexpected effect of the composition has not been compared with respect to the closest prior art composition. Specifically, the Examining Division stated that "[t]here should, therefore, be an improvement not when compared with any prior art compositions but when compared with the composition of the closest prior art." (Communication of 16 May 2017, page 4).

Applicant maintains that a comparison of the invention with the closest prior art has been presented in the application as filed.

The Examining Division states that D6 is considered to be the closest prior art to the subject matter of claim 1 (Communication of 16 May 2017, page 2, 3.2). D6 appears to only specifically disclose two nasal formulation preparations: diazepam solutions comprising alpha-tocopherol/vitamin E, and dehydrated ethanol and diazepam suspensions comprising vitamin E TPGS, propylene glycol, and water. The suspension formulation of document D6, Table 4-1 is nearly identical to the comparative suspension of present application, Table 11-2:

TABLE 4-1

Diazepam Suspension Formulations

Component	Suspension 03 (200 mg/mL Diazepam) Concentration (mg/mL)	Suspension 01 (100 mg/mL Diazepam) Concentration (mg/mL)
Diazepam USP	200.00	100.00
Vitamin E Polyethylene Glycol Succinate NF	100.0	100.0
Methylparaben NF	2.0	2.0
Propylparaben NF	0.5	0.5
Propylene Glycol USP	100.0	100.0
Povidone USP/NF	25.0	25.0
Purified Water USP/EP	q.s. to 1 mL	q.s. to 1 mL

Table 11-2 of the current application:

Component	Function	Concentration (mg/mL)
Diazepam	Active	100.0
Methyl Paraben	Preservative	2.0
Propyl Paraben	Preservative	0.5
Intravail A3	Absorption aid	2.5
Vitamin E TPGS	Dispersant	10.0
Propylene Glycol	Dispersant	100.0
Povidone	Suspending agent	5.0
Water	Carrier	q.s. to 1.0 mL

The person of skill in the art would appreciate that both formulations contain diazepam, vitamin E, methylparaben, propylparaben, propylene glycol, povidone, and water. The person of skill in the art would know that parabens are preserving agents, and thus do not contribute to a formulation's bioavailability. Therefore, the presence of methylparaben and propylparaben are not relevant when discussing bioavailability of a formulation. Therefore, the relevant components of the diazepam suspension of D6, Table 4-1, and present application, Table 11-2, are diazepam, vitamin E, propylene glycol, povidone, and water. The skilled artisan would understand that propylene glycol, povidone, and water combine to form a suspension. Thus, these compounds form the co-solvent system of D6, Table 4-1, and Table 11-2 of the instant specification.

Applicant thus submits that the skilled artisan would have identified D6, Table 4-1, as the closest-state-of-the-art formulation to the instant claims, because the diazepam suspension of D6, Table 4-1 is a nasal formulation of diazepam, vitamin E, and a co-solvent system, and the diazepam solution of the current claims is a nasal formulation of diazepam, vitamin E, a co-solvent system, and an alkyl glycoside. To this point, the Examining Division acknowledges that the subject-matter of claim 1 differs from D6 at least in the selection of a specific co-solvent system: ethanol and benzyl alcohol. (Communication of 16 May 2017, page 2, 3.2).

Applicant notes that the subject matter of claim 1 also differs from D6, Table 4-1 by the inclusion of an alkyl glycoside. The diazepam suspension of Table 11-2 bridges the gap between closest-prior-art formulation of D6, Table 4-1 and the current claims, because Table 11-2 includes Intravail A3 (i.e. alkyl glycoside) in the formulation, whereas Table 4-1 does not.

Accordingly, the suspension of Table 11-2 is even closer to the claimed subject-matter than is D6.

Intravail A3 (i.e. alkyl glycoside) is a penetration enhancer, added to enhance absorption of diazepam across the nasal mucosa. As the instantly claimed benzodiazepine solution contains an alkyl glycoside and the diazepam suspension of Table 11-2 also contains an alkyl glycoside (i.e. Intravail A3), Table 11-2 only differs from the instant claims by way of the co-solvent system. Therefore, the suspension of Table 11-2 is suitable for comparison to the current claims, because the only difference between Table 11-2 and the closest-prior-art formulation (i.e. D6, Table 4-1) is the presence of an alkyl glycoside and the only difference between Table 11-2 and the instant claims is the co-solvent system.

Therefore, when comparing the closest-prior-art diazepam suspension to the instant claims, alkyl glycoside is eliminated as a variable affecting bioavailability, and the co-solvent system of 1-25% ethanol and 1-25% benzyl alcohol has the technical effect of increasing bioavailability of benzodiazepines.

IV Auxiliary Request 1

The optional additional presence of further APIs and excipients (which has been defined in the Main Request) has been deleted, for the unexpected event that the Examining Division does not accept this amendment.

V Auxiliary Request 2

Compared with Auxiliary Request 1, the amounts of alcohols have been further limited to tailor the claims towards the examples (see e.g., the solution in Table 11-1).

Accordingly, it is even more credible that the claimed improvement is provided over the whole claim scope.

Dr. Hendrik Wichmann
European Patent Attorney

Enclosures
Main and Auxiliary Requests 1 and 2 (markup and clean copies)
Amended specification pages 1-55 - numbering refers to clean copy (markup and clean copies)

Europäisches Patentamt
European Patent Office
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Letter accompanying subsequently filed items

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The document(s) listed below is (are) subsequently filed documents pertaining to the following application:

Application number	12801372.9
Applicant's or representative's reference	EPA-124 519

	Description of document	Original file name	Assigned file name
1	Amended description (clean copy)	EPA-124519_specification (clean).pdf	DESC-1.pdf
2	Amended description with annotations	EPA-124519_specification (markup).pdf	DESC-HWA-1.pdf
3	Amended claims (clean copy)	EPA-124519_claims MR (clean).pdf	CLMS-1.pdf
4	Amended claims with annotations	EPA-124519_claims MR (markup).pdf	CLMS-HWA-1.pdf
5	Amended claims (clean copy)	EPA-124519_claims AR1(clean).pdf	CLMS-2.pdf
6	Amended claims with annotations	EPA-124519_claims AR1(markup).pdf	CLMS-HWA-2.pdf
7	Amended claims (clean copy)	EPA-124519_claims AR2 (clean).pdf	CLMS-3.pdf
8	Amended claims with annotations	EPA-124519_claims AR2(markup).pdf	CLMS-HWA-3.pdf
9	Letter dealing with Oral proceedings	EPA-124519_response.pdf	ORAL-1.pdf

	Payment	
1	Mode of payment	Not specified

Signatures

Place:	**Munich**
Date:	**02 November 2017**
Signed by:	**/Dr. Hendrik Wichmann, European Patent Attorney/**
Representative name:	**Hendrik WICHMANN**
Capacity:	**(Representative)**

ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

FIELD OF THE INVENTION

[001] This application relates to the nasal administration of benzodiazepine drugs and combinations thereof.

BACKGROUND OF THE INVENTION

[002] By way of non-limiting example, the benzodiazepine family consists of drugs such as diazepam, lorazepam, and midazolam. The drugs in this family have been observed as possessing sedative, tranquilizing and muscle relaxing properties. They are frequently classified as anxiolytic and skeletal muscle relaxants. They are thought to be useful in preventing, treating, or ameliorating the symptoms of anxiety, insomnia, agitation, seizures (such as those caused by epilepsy), muscle spasms and rigidity, the symptoms of drug withdrawal associated with the continuous abuse of central nervous system depressants, and exposure to nerve agents.

[003] Benzodiazepines are thought to act by binding to the $GABA_A$ receptor of a neuron, possibly causing the receptor to change shape and making it more accessible to gama-aminobutyric acid (GABA).

[004] GABA is an inhibitory neurotransmitter that, when bound to the $GABA_A$ receptor, facilitates Cl^- ions flooding into the neuron to which the receptor is bound. The increase in Cl^- ions hyperpolarizes the membrane of the neuron. This completely or substantially reduces the ability of the neuron to carry an action potential. Targeting this receptor is particularly useful in treating many disorders, such as tetanus and epilepsy, which may result from too many action potentials proceeding through the nervous system.

[005] Current formulations of benzodiazepine drugs can be administered orally, rectally, or parenterally. The ability to utilize these and other types of formulations has been significantly limited due, in many cases, to solubility challenges.

[006] The oral route of administration may be considered sub-optimal due to several disadvantages. For example, the amount of time required for an orally administered benzodiazepine drug to reach therapeutically relevant concentrations in blood plasma may be rather long, such as an hour or more. Moreover, as benzodiazepine drugs pass through the liver a significant amount of the drug may be metabolized. Thus, large doses may be required to achieve therapeutic plasma levels. Furthermore, due to the nature of seizures and muscle spasms, it can be extremely difficult for either a patient or a care-giver to administer the benzodiazepine drug orally and care-givers may be reluctant to place their hands in patients' mouths.

[007] Intravenous administration perhaps provides a faster route of administration. However intravenous administration is generally limited to trained health care professionals in tightly controlled clinical settings. Additionally, sterility must be maintained. Furthermore, administering any drug intravenously can be painful and is likely impractical for patients suffering from a phobia of needles. In addition, intravenous administration of benzodiazepines is associated with respiratory depression. Thus, use of intravenous benzodiazepines is limited to professional health care environments.

[008] Rectal suppository compositions of benzodiazepine drugs can have a rapid onset of action. However, the inconvenience of rectally administered drug 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 care-givers.

SUMMARY OF THE INVENTION

[009] The invention refers to a pharmaceutical solution for use in a method of treating seizures by nasal administration of said pharmaceutical solution which consists of: (a) a benzodiazepine drug; (b) one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from 30% to 95% (w/w); (c) 1-25% (w/v) ethanol and 1-25% (w/v) benzyl alcohol, in a combined amount from 10% to 50% (w/w); and (d) an alkyl glycoside.

[010] In some embodiments, there are provided (non-aqueous) pharmaceutical solutions as defined in the claims for use as defined in the claims for administration to one or more nasal mucosal membranes of a patient. The benzodiazepine drug is dissolved in the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); and the one or more alcohols as defined in the claims. In some embodiments, the benzodiazepine drug is selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, any pharmaceutically-acceptable salts thereof, and any combinations thereof. In some embodiments, the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof. In some embodiments, the solution contains about 1 to about 20 % (w/v) of benzodiazepine, e.g. about 1 to about 20 % (w/v) of diazepam. In some embodiments, the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ- tocotrienol, δ- tocotrienol, tocophersolan, any isomers thereof, any esters thereof, any analogs or derivatives thereof, and any combinations thereof. . The solution contains ethanol (1-25 % (w/v)) and benzyl alcohol (1-25 % (w/v)), or ethanol (10-22.5 % (w/v)) and benzyl alcohol (7.5-12.5 % (w/v)), wherein the combined amounts are 10% to 50%. In some embodiments, the benzodiazepine is present in the pharmaceutical composition in a concentration from about 20 mg/mL to about 200 mg/mL. In some embodiments, the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from about 45% to about 85% (w/w). In some embodiments, the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from about 50% to about 75% (w/w). In some embodiments, the alcohols are in an amount from about 15% to 50% (w/w), e.g. about 25% to about 40% (w/w). In some embodiments, the solution consists of diazepam (5-15 % (w/v)), alkyl glycoside (0.01-1 % (w/v)), vitamin E (45-65 % (w/v)), ethanol (10-25 % (w/v)) and benzyl alcohol (5-15 % (w/v)). In some embodiments, the solution comprises at least about 0.01% (w/w) of an alkyl glycoside, *e.g.* about 0.01% to 1% (w/w) of an alkyl glycoside, such as dodecyl maltoside. In some embodiments, the solution consists of

diazepam (5-15 % (w/v)), dodecyl maltoside (0.01-1 % (w/v)), vitamin E (45-65 % (w/v)), ethanol (10-25 % (w/v)) and benzyl alcohol (5-15 % (w/v)); more particularly the solution may consist of diazepam (9-11 % (w/v)), dodecyl maltoside (0.1-0.5 % (w/v)), vitamin E (50-60 % (w/v)), ethanol (15-22.5 % (w/v)) and benzyl alcohol (7.5-12.5 % (w/v)); and even more particularly, the solution may consist of diazepam (10 % (w/v)), dodecyl maltoside (0.15-0.3 % (w/v)), vitamin E (50-60 % (w/v)), ethanol (17-20 % (w/v)) and benzyl alcohol (10-12 % (w/v)).

[011] The pharmaceutical solution is for use in a method of treating a patient with a disorder which may be treatable with a benzodiazepine drug, comprising: administering to one or more nasal mucosal membranes of a patient said pharmaceutical solution for nasal administration. In some embodiments, the benzodiazepine drug is dissolved in the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); and the alcohols as defined in the claims. In some embodiments, the benzodiazepine is present in the pharmaceutical composition in a concentration from about 20 mg/mL to about 200 mg/mL. In some embodiments, the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from about 45% to about 85% (w/w). In some embodiments, the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from about 50% to about 75% (w/w). In some embodiments, the solution consists of diazepam (5-15 % (w/v)), alkyl glycoside (0.01-1 % (w/v)), vitamin E (45-65 % (w/v)), ethanol (10-25 % (w/v)) and benzyl alcohol (5-15 % (w/v)). In some embodiments, the solution comprises at least about 0.01% (w/w) of an alkyl glycoside, *e.g.* about 0.01% to 1% (w/w) of an alkyl glycoside, such as dodecyl maltoside. In some embodiments, the solution consists of diazepam (5-15 % (w/v)), dodecyl maltoside (0.01-1 % (w/v)), vitamin E (45-65 % (w/v)), ethanol (10-25 % (w/v)) and benzyl alcohol (5-15 % (w/v)); more particularly the solution may consist of diazepam (9-11 % (w/v)), dodecyl maltoside (0.1-0.5 % (w/v)), vitamin E (50-60 % (w/v)), ethanol (15-22.5 % (w/v)) and benzyl alcohol (7.5-12.5 % (w/v)); and even more particularly, the solution may consist of diazepam (10 % (w/v)), dodecyl maltoside (0.15-0.3 % (w/v)), vitamin E (50-60 % (w/v)), ethanol (17-20 % (w/v)) and benzyl alcohol (10-12 % (w/v)). In some embodiments, the patient is human. In some embodiments, the benzodiazepine is administered in a therapeutically effective amount from about 1 mg to about 20 mg. In some embodiments, the benzodiazepine is administered as in a dosage volume from about 10 µL to about 200 µL. In some embodiments, the administration of the pharmaceutical composition comprises spraying at least a portion of the therapeutically effective amount of the benzodiazepine into at least one nostril. In some embodiments, the administration of the pharmaceutical composition comprises spraying at least a portion of the therapeutically effective amount of the benzodiazepine into each nostril. In some embodiments, administration of the pharmaceutical composition comprises spraying a first quantity of the pharmaceutical composition into the first nostril, spraying a second quantity of the pharmaceutical composition into a second nostril, and optionally after a pre-selected time delay, spraying a third quantity of the pharmaceutical composition into the first nostril. In some embodiments, the method further comprises, optionally after a pre-selected time delay, administering at least a fourth quantity of the pharmaceutical composition to the second nostril. In some embodiments, nasal administration of the pharmaceutical

composition begins at any time before or after onset of symptoms of a disorder which may be treatable with the pharmaceutical composition. In some embodiments, the treatment achieves bioavailability that is from about 80-125% (e.g. about 90-110%, or more particularly about 92.5-107.5%) of that achieved with the same benzodiazepine administered intravenously, e.g. In this context, it is intended that bioavailability be determined by a suitable pharmacodynamic method, such as comparison of area under the blood plasma concentration curve (AUC) for the nasally and intravenously administered drug. It is further understood that the percent bioavailability of the nasally administered benzodiazepine may be determined by comparing the area under the blood plasma concentration curve obtained with one dose of the benzodiazepine (e.g. 10 mg of nasal diazepam) with another dose of the same benzodiazepine administered intravenously (e.g. 5 mg of i.v. diazepam), taking into consideration the difference in dose. Thus, for the sake of illustration, a 10 mg nasal diazepam dose that achieves an AUC that is precisely half of the AUC obtained with 5 mg of i.v. diazepam would have a bioavailability of 100%. In some embodiments, the disorder to be treated is a seizure, such as an epileptic seizure, a breakthrough seizure, or other seizure. In some embodiments, the solution and treatment with the solution are substantially non-irritating and well-tolerated.

[012] In some embodiments, the benzodiazepine drug is dissolved in a carrier system. In some embodiments, at least part of the benzodiazepine drug is in a form comprising benzodiazepine microparticles, nanoparticles or combinations thereof. In some embodiments, the composition is substantially free of benzodiazepine microparticles, nanoparticles or combinations thereof.

[013] In some embodiments, the benzodiazepine drug is selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, any pharmaceutically-acceptable salts thereof, and any combinations thereof. In some embodiments, the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof. In some embodiments, the benzodiazepine drug comprises benzodiazepine microparticles, nanoparticles, or combinations thereof. In some embodiments, the benzodiazepine nanoparticles have an effective average particle size of less than about 5000 nm. In some embodiments, the benzodiazepine drug is substantially free of benzodiazepine microparticles, nanoparticles or combinations thereof.

[014] In some embodiments, the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ- tocotrienol, δ- tocotrienol, tocophersolan, any isomers thereof, any esters thereof, any analogs or derivatives thereof, and any combinations thereof. In some embodiments, a synthetic tocopherol can include Vitamin E TPGS (Vitamin E polyethylene glycol succinate). In some embodiments, on the other hand, synthetic tocopherols exclude tocopherols covalently bonded or linked (e.g. through a diacid linking group) to a glycol polymer, such as polyethylene glycol). Thus, in some embodiments, the compositions described herein exclude Vitamin E TPGS.

[015] In some embodiments, the benzodiazepine drug is present in the carrier system in a concentration from about 1 mg/mL to about 600 mg/mL. In some embodiments, the benzodiazepine drug is present in a carrier system in a concentration from about 10 mg/mL to about 250 mg/mL. In some embodiments, the benzodiazepine is present in a carrier system in a concentration from about 20 mg/mL to about 50 mg/mL.

[016] In some embodiments, the carrier system comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 45% to about 85% (w/w). In some embodiments, the carrier system comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 60% to about 75% (w/w). In some embodiments, the carrier system comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount of about 70% (w/w).

[017] In some embodiments, the carrier system comprises said alcohols or glycols in an amount from about 15% to 50% (w/w). In some embodiments, the carrier system comprises said alcohols in an amount from about 25% to about 40% (w/w). In some embodiments, the carrier system comprises said alcohols in an amount of about 30% (w/w).

[018] In some embodiments, the composition comprises at least one additional ingredient selected from the group consisting of: active pharmaceutical ingredients; and excipients, such as enhancers and agents used to adjust the pH, buffer the composition, prevent degradation, and improve appearance, odor, or taste.

[019] In some embodiments, the composition comprises one or more additional excipients, such as one or more parabens, one or more povidones, and/or one or more alkyl glycosides.

[020] The pharmaceutical solution is for use in a method of treating a patient with a disorder that may be treatable with a benzodiazepine drug as defined in the claims. In some embodiments, the patient is a human. In some embodiments, the benzodiazepine drug includes benzodiazepine microparticles, nanoparticles, or combinations thereof. In some embodiments, the composition is substantially free of benzodiazepine microparticles, nanoparticles or combinations thereof.

[021] In some embodiments, the benzodiazepine drug is selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, or any pharmaceutically-acceptable salts thereof, and any combinations thereof. In some embodiments, the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof. In some embodiments, the benzodiazepine drug is fully dissolved in a single phase comprising one or more one or more natural or synthetic tocopherols or tocotrienols and one or more alcohols or glycols. In some embodiments, the benzodiazepine drug comprises benzodiazepine microparticles, nanoparticles, or combinations thereof. In some such embodiments, the composition further comprises water. In some embodiments, the benzodiazepine nanoparticles have an effective average particle size of less than about 5000 nm. In some embodiments, the composition is substantially free of benzodiazepine microparticles, nanoparticles or combinations thereof.

[022] In some embodiments, the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ- tocotrienol, δ- tocotrienol, tocophersolan, any isomers thereof, any esters thereof, any analogs or derivatives thereof, and any combinations thereof.

[023] In some embodiments, the pharmaceutical solution contains one or more glycols which can be selected from the group consisting of: ethylene glycol, propylene glycol, butylene glycol, pentylene glycol, any isomers thereof, and any combinations thereof. In some embodiments, the alcohol or glycol is free of water (dehydrated, USP). In some embodiments, the alcohol is ethanol (dehydrated, USP).

[024] In some embodiments, the benzodiazepine drug is present in the carrier system in a concentration from about 1 mg/mL to about 600 mg/mL. In some embodiments, the benzodiazepine drug is present in the carrier system in a concentration of from about 10 mg/mL to about 250 mg/mL. In some embodiments, the benzodiazepine drug is present in the carrier system in a concentration of from about 20 mg/mL to about 50 mg/mL.

[025] In some embodiments, the carrier system comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 45% to about 85% (w/w). In some embodiments, the carrier system comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 60% to about 75% (w/w). In some embodiments, the carrier system comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount of about 70% (w/w).

[026] In some embodiments, the composition comprises at least one additional ingredient selected from the group consisting of: active pharmaceutical ingredients; enhancers; excipients; and agents used to adjust the pH, buffer the composition, prevent degradation, and improve appearance, odor, or taste.

[027] In some embodiments, the composition is in a pharmaceutically-acceptable spray formulation, and further comprising administering the composition to one or more nasal mucosal membranes of the patient. In some embodiments, the therapeutically effective amount is from about 1 mg to about 20 mg of the benzodiazepine. In some embodiments, the pharmaceutical composition is in a pharmaceutically-acceptable spray formulation having volume from about 10 µL to 200 µL.

[028] In some embodiments, the administration of the composition comprises spraying at least a portion of the therapeutically effective amount of the composition into at least one nostril. In some embodiments, the administration of the composition comprises spraying at least a portion of the therapeutically effective amount of the composition into each nostril. In some embodiments, the administration of the composition comprises spraying a first quantity of the composition into the first nostril, spraying a second quantity of the composition into a second nostril, and optionally after a pre-selected time delay, spraying a third quantity of the composition into the first nostril. Some embodiments further comprise, optionally after a pre-selected time delay, administering at least a fourth quantity of the composition to the second nostril.

[029] In some embodiments, the administration of the composition begins at any time before or after onset of symptoms of a disorder which may be treatable with the composition.

[030] Additional advantages of the invention will become apparent to the person skilled in the art upon consideration of the disclosure set forth herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[031] Some embodiments of the invention may be further appreciated upon consideration of the appended drawings, of which:

[032] Figure 1 depicts a 240 hour linear plot of the arithmetic mean plasma concentration of diazepam after intranasal administration of 10 mg of diazepam as a suspension of Table 11-2, intranasal administration 10 mg of diazepam as a solution of Table 11-1, and 5 mg of diazepam as an intravenous injection.

[033] Figure 2 depicts a 240 hour semi-logarithmic plot of the arithmetic mean plasma concentration of diazepam after intranasal administration of 10 mg of diazepam as a suspension of Table 11-2, intranasal administration 10 mg of diazepam as a solution of Table 11-1, and 5 mg of diazepam as an intravenous injection.

[034] Figure 3 depicts a 24 hour linear plot of the arithmetic mean plasma concentration of diazepam after intranasal administration of 10 mg of diazepam as a suspension of Table 11-2, intranasal administration 10 mg of diazepam as a solution of Table 11-1, and 5 mg of diazepam as an intravenous injection.

[035] Figure 4 is a Flow Diagram for one embodiment of a process for the manufacture of a diazepam solution according to the instant invention.

[036] Figure 5 is a Flow Diagram for one embodiment of a process for the manufacture of a diazepam suspension according to the instant invention.

DETAILED DESCRIPTION OF THE INVENTION

[037] Provided herein are pharmaceutical compositions of one or more benzodiazepine drugs for use in methods as defined in the claims. Such pharmaceutical compositions are administered nasally.

[038] In some embodiments, the benzodiazepine drug is selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, any pharmaceutically-acceptable salts thereof, and any combinations thereof. In some embodiments, the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof. In some embodiments, the benzodiazepine drug comprises benzodiazepine microparticles, nanoparticles, or combinations thereof. In some embodiments, the benzodiazepine nanoparticles have an effective average particle size of less than about 5000 nm. In some embodiments, the composition is substantially free of benzodiazepine microparticles, nanoparticles or combinations thereof.

[039] In some embodiments, the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ- tocotrienol, δ- tocotrienol, tocophersolan, any isomers thereof, any esters thereof, any analogs or derivatives thereof, and any combinations thereof. In some embodiments, the carrier system includes one or

more synthetic tocopherols having a polymer glycol covalently bonded or linked to a tocopherol core, such as Vitamin E TPGS, which is described in United States Patent No. 6,193,985. In particular, it has been found that in some particulate suspensions of benzodiazepines, wherein the benzodiazepine is not dissolved in a tocopherol phase, Vitamin E TPGS can be a desirable excipient for stabilizing the particulate (microparticle, nanoparticle or combination) suspension. In some embodiments, on the other hand, the carrier system specifically excludes synthetic tocopherols having a polymer glycol covalently bonded or linked to a tocopherol core, such as Vitamin E TPGS, which is described in United States Patent No. 6,193,985.

[040] One alcohol is ethanol (dehydrated, USP). In some embodiments, the one or more additional glycols are selected from the group consisting of: ethylene glycol, propylene glycol, butylene glycol, pentylene glycol, any isomers thereof, and any combinations thereof. In some embodiments, the glycol is propylene glycol USP. In some embodiments, a synthetic tocopherol can include Vitamin E TPGS (Vitamin E polyethylene glycol succinate). In some embodiments, on the other hand, synthetic tocopherols exclude tocopherols covalently bonded or linked (e.g. through a diacid linking group) to a glycol polymer, such as polyethylene glycol). Thus, in some embodiments, the compositions described herein exclude Vitamin E TPGS.

[041] In some embodiments, the benzodiazepine drug is present in the carrier system in a concentration from about 1 mg/mL to about 600 mg/mL. In some embodiments, the benzodiazepine drug is present in a carrier system in a concentration from about 10 mg/mL to about 250 mg/mL. In some embodiments, the benzodiazepine is present in a carrier system in a concentration from about 20 mg/mL to about 50 mg/mL.

[042] In some embodiments, the carrier system comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 45% to about 85% (w/w). In some embodiments, the carrier system comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 60% to about 75% (w/w). In some embodiments, the carrier system comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount of about 70% (w/w). In some embodiments, a synthetic tocopherol can include Vitamin E TPGS (Vitamin E polyethylene glycol succinate). In some embodiments, on the other hand, synthetic tocopherols exclude tocopherols covalently bonded or linked (e.g. through a diacid linking group) to a glycol polymer, such as polyethylene glycol). Thus, in some embodiments, the compositions described herein exclude Vitamin E TPGS.

[043] The carrier system comprises said alcohols in an amount from 10% to 50%, 10% to about 40%, 10% to about 35%, about 12% to 50%, about 12% to about 40%, about 12% to about 35%, about 15% to 50%, about 15% to about 40%, about 15% to about 35%, 10%, about 12.5%, about 15%, about 17.5%, about 20%, about 22.5%, about 25%, about 27.5%, about 30%, about 32.5%, about 35%, about 37.5%, about 40%, about 42.5%, about 45%, about 47.5%, 50%(w/w). In some embodiments, the carrier system comprises said alcohols in an amount from about 25% to about 40% (w/w). In some embodiments, the carrier system comprises one or more alcohols or glycols, or any combinations thereof, in an amount of about 30% (w/w). In some preferred embodiments, the glycols exclude glycol polymers. In some preferred embodiments, the

glycols exclude glycol polymers having an average molecular weight of greater than 200. In some embodiments, the glycols exclude polyethylene glycol having an average molecular weight of greater than about 200.

[044] In some embodiments, the carrier system comprises said alcohols in an amount from about 15% to 50% (w/w). In some embodiments, the carrier system comprises said alcohols in an amount from about 25% to about 40% (w/w). In some embodiments, the carrier system comprises said alcohols in an amount of about 30% (w/w).

[045] In some embodiments, the composition comprises at least one additional ingredient selected from the group consisting of: active pharmaceutical ingredients; enhancers; excipients; and agents used to adjust the pH, buffer the composition, prevent degradation, and improve appearance, odor, or taste.

[046] In some embodiments, the compositions comprise at least one alkyl glycoside. In some embodiments, the at least one alkyl glycoside is one described in United States Patent No. 5,661,130.

[047] In some embodiments, the composition comprises a benzodiazepine drug that is fully dissolved in a solvent comprising a natural or synthetic tocopherol or tocotrienol, and an alcohol or glycol. In some embodiments, the composition comprises a benzodiazepine drug that is fully dissolved in a solvent comprising a natural or synthetic tocopherol or tocotrienol and said alcohols, wherein the solution is at least substantially free of water. (In some embodiments, "substantially free of water" indicates that the solution contains less than about 1%, less than about 0.5%, less than about 0.25% or less than about 0.1% water.) In some embodiments, the composition consists essentially of a benzodiazepine drug that is fully dissolved in a solvent consisting of one or more natural or synthetic tocopherols or tocotrienols, one or more alcohols or glycols, and one or more alkyl glycosides as defined in the claims. In some embodiments, the composition consists essentially of a benzodiazepine drug that is fully dissolved in a solvent consisting of one or more natural or synthetic tocopherols or tocotrienols, one or more alcohols or glycols, and optionally one or more alkyl glycosides as defined in the claims wherein the solution is at least substantially free of water. (In some embodiments, "substantially free of water" indicates that the solution contains less than about 1%, less than about 0.5%, less than about 0.25% or less than about 0.1% water.) In some embodiments, the composition consists of a benzodiazepine dissolved in a solvent consisting of one or more natural or synthetic tocopherols or tocotrienols, one or more alcohols or glycols, and one or more alkyl glycosides as defined in the claims. In some embodiments, the composition consists of a benzodiazepine dissolved in a solvent consisting of one or more natural or synthetic tocopherols or tocotrienols, one or more alcohols or glycols, and one or more alkyl glycosides as defined in the claims, wherein the solution is at least substantially free of water. (In some embodiments, "substantially free of water" indicates that the solution contains less than about 1%, less than about 0.5%, less than about 0.25% or less than about 0.1% water.)

[048] In some embodiments, the composition comprises a benzodiazepine drug that is fully dissolved in a solvent comprising a natural or synthetic tocopherol or tocotrienol, and an alcohol or glycol as defined in the claims. Thus, in some embodiments, the composition is substantially free of benzodiazepine microparticles, nanoparticles or combinations thereof. In some embodiments, the composition comprises a benzodiazepine

drug that is fully dissolved in a solvent comprising a natural or synthetic tocopherol or tocotrienol and an alcohol or glycol as defined in the claims, wherein the solution is at least substantially free of water. (In some embodiments, "substantially free of water" indicates that the solution contains less than about 1%, less than about 0.5%, less than about 0.25% or less than about 0.1% water.) In some embodiments, the composition consists essentially of a benzodiazepine drug that is fully dissolved in a solvent consisting of one or more natural or synthetic tocopherols or tocotrienols, one or more alcohols or glycols, and one or more alkyl glycosides as defined in the claims. In some embodiments, the composition consists essentially of a benzodiazepine drug that is fully dissolved in a solvent consisting of one or more natural or synthetic tocopherols or tocotrienols, one or more alcohols or glycols, and one or more alkyl glycosides as defined in the claims wherein the solution is at least substantially free of water. (In some embodiments, "substantially free of water" indicates that the solution contains less than about 1%, less than about 0.5%, less than about 0.25% or less than about 0.1% water.) In some embodiments, the composition consists of a benzodiazepine dissolved in a solvent consisting of one or more natural or synthetic tocopherols, one or more alcohols or glycols, and one or more alkyl glycosides as defined in the claims. In some embodiments, the composition consists of a benzodiazepine dissolved in a solvent consisting of one or more natural or synthetic tocopherols, one or more alcohols or glycols, and one or more alkyl glycosides as defined in the claims, wherein the solution is at least substantially free of water. (In some embodiments, "substantially free of water" indicates that the solution contains less than about 1%, less than about 0.5%, less than about 0.25% or less than about 0.1% water.)

[049] Disclosed is a composition which contains a benzodiazepine drug that at least partially in a particulate form suspended in a carrier system containing a natural or synthetic tocopherol or tocotrienol and one or more alcohols or glycols. Disclosed is that substantially all the benzodiazepine drug is in a particulate form. Disclosed is that at least part of the benzodiazepine drug is in a microparticulate or nanoparticulate form. The carrier system is one in which the amount of at least one benzodiazepine present in the composition exceeds its solubility in the carrier system. A carrier system in such a composition can include water. Such a liquid carrier system can contain water and one or more excipients. One or more excipients can be dissolved or suspended in the carrier system. The composition can comprises a benzodiazepine drug in a form including benzodiazepine microparticles and/or nanoparticles suspended in a carrier system comprising synthetic tocopherol, one or more parabens, one or more alcohols or glycols, one or more surfactants and water. The composition can consists essentially of a benzodiazepine drug in a form including benzodiazepine microparticles and/or nanoparticles suspended in a carrier system consisting essentially of a synthetic tocopherol, one or more parabens, one or more alcohols or glycols, one or more surfactants and water. The composition can consist of a benzodiazepine drug in a form including benzodiazepine microparticles and/or nanoparticles suspended in a carrier system consisting of a synthetic tocopherol, one or more parabens, one or more alcohols or glycols, one or more surfactants and water. Disclosed is a composition which contains a benzodiazepine drug that at least partially in a particulate form suspended in a carrier system containing a natural or synthetic tocopherol or tocotrienol, one or more alcohols or glycols, and an alkyl glycoside.

Substantially all the benzodiazepine drug can be in a particulate form. At least part of the benzodiazepine drug is in a microparticulate or nanoparticulate form. The carrier system is one in which the amount of at least one benzodiazepine present in the composition exceeds its solubility in the carrier system. A carrier system in such a composition can include water. Such a liquid carrier system can contain water and one or more excipients. One or more excipients can be dissolved or suspended in the carrier system. At least one such excipient can stabilize the suspension of benzodiazepine particulates in the carrier system. Benzodiazepine particulate suspensions can specifically exclude one or more polymeric glycols, such as polyethylene glycol. Benzodiazepine particulate suspensions can specifically exclude one or more polymeric glycols having a molecular weight greater than about 200 g/mol. The composition can comprise a benzodiazepine drug in a form including benzodiazepine microparticles and/or nanoparticles suspended in a carrier system comprising a synthetic tocopherol, one or more parabens, one or more alcohols or glycols, an alkyglycoside and water. The composition consists essentially of a benzodiazepine drug in a form including benzodiazepine microparticles and/or nanoparticles suspended in a carrier system consisting essentially of a synthetic tocopherol, one or more parabens, one or more alcohols or glycols, an alkyl glycoside, optionally a surfactant, and water. The composition can consist of a benzodiazepine drug in a form including benzodiazepine microparticles and/or nanoparticles suspended in a carrier system consisting of a synthetic tocopherol, one or more parabens, one or more alcohols or glycols, an alkyl glycoside, optionally one or more surfactants, and water.

[050] The invention also discloses a method of treating a patient with a disorder that may be treatable with a benzodiazepine drug. In some embodiments, the patient is a human. In some embodiments, the method comprises: administering to one or more nasal mucosal membranes of a patient a pharmaceutical composition for nasal administration as defined in the claims.

[051] In some embodiments, the benzodiazepine drug is selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, or any pharmaceutically-acceptable salts thereof, and any combinations thereof. In some embodiments, the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof. In some embodiments, the benzodiazepine drug comprises benzodiazepine microparticles, nanoparticles, or combinations thereof. In some embodiments, the benzodiazepine nanoparticles have an effective average particle size of less than about 5000 nm.

[052] In some embodiments, the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ- tocotrienol, δ-tocotrienol, tocophersolan, any isomers thereof, any esters thereof, any analogs or derivatives thereof, and any combinations thereof. A synthetic tocopherol may include a tocopherol that has been modified to include a hydrophilic group, such as a polyethylene glycol group, which may be directly covalently bonded to the tocopherol or may be linked to the tocopherol through a covalent linking group, such as a diacid. An exemplary synthetic tocopherol of this type is Vitamin E Polyethylene Glycol Succinate

(Vitamin E TPGS), although the person skilled in the art will be able to envision other synthetic tocopherols that have similar diacid and/or hydrophilic groups.

[053] In some embodiments, one or more glycols are present as excipients and are selected from the group consisting of: ethylene glycol, propylene glycol, butylene glycol, pentylene glycol, any isomers thereof, and any combinations thereof. In some embodiments, one or more glycols specifically excludes polymeric glycols, such as polyethylene glycol. In some embodiments, one or more glycols specifically excludes a polymeric glycol having a molecular weight of greater than about 200 g/mol.

[054] In some embodiments, the benzodiazepine drug is present in the carrier system in a concentration from about 1 mg/mL to about 600 mg/mL. In some embodiments, the benzodiazepine drug is present in the carrier system in a concentration of from about 10 mg/mL to about 250 mg/mL. In some embodiments, the benzodiazepine drug is present in the carrier system in a concentration of from about 20 mg/mL to about 50 mg/mL.

[055] In some embodiments, the carrier system comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 45% to about 85% (w/w). In some embodiments, the carrier system comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 60% to about 75% (w/w). In some embodiments, the carrier system comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount of about 70% (w/w). In some embodiments, especially where particulate suspensions of a benzodiazepine drug are contemplated, the compositions may include a tocopherol, especially a synthetic tocopherol having a hydrophilic group covalently linked to a tocopherol. In other embodiments, especially where a solution of benzodiazepine drug is contemplated, the tocopherol is substantially or completely free of Vitamin E TPGS.

[056] In some embodiments, the composition comprises at least one additional ingredient selected from the group consisting of: active pharmaceutical ingredients; enhancers; excipients; and agents used to adjust the pH, buffer the composition, prevent degradation, and improve appearance, odor, or taste.

[057] In some embodiments, a composition comprises at least one penetration enhancer in addition to a benzodiazepine drug, a natural or synthetic tocopherol or tocotrienol, and an alcohol or glycol. In some embodiments, the penetration enhancer is an alkyl glycoside. In some embodiments, the alkyl glycoside refers to any sugar joined to any hydrophobic alkyl, as described in United States patent number 5,661,130. The hydrophobic alkyl can be any suitable length, for example about 9 to about 24 carbons in length, especially about 10 to about 14 carbons in length. The hydrophobic alkyl can be branched and/or partially or wholly unsaturated. The alkyl may be joined to the saccharide core for example through a carbonyl group, whereby an ester group may be formed. A suitable alkyl glycoside will have the characteristics of being nontoxic, nonionic, and capable of increasing the absorption of a benzodiazepine drug when it is administered intranasally as described herein. Exemplary saccharides that may be covalently joined to an alkyl according to the present invention include glucose, maltose, maltotriose, maltotetrose, sucrose and trehalose. Exemplary alkyl glycosides that may be employed include octyl-, nonyl-, decyl-, undecyl-, dodecyl, tridecyl, tetradecyl,

pentadecyl, octadecyl α- or β-D-maltoside, -glucoside or sucroside. In some embodiments, the preferred glycosides include maltose, sucrose or glucose linked by glycosidic linkage to an alkyl chain of 9, 10, 12, 14, 16, 18 or 20 carbon atoms. Where present, the amount of alkyl glycoside in the composition is sufficient to enhance the absorption of a benzodiazepine drug administered by the intranasal route. In some embodiments, the amount of alkyl glycoside in the composition is selected so as to enhance absorption of the benzodiazepine drug, while at the same time not significantly irritating the nasal mucosa. In some embodiments, the amount of alkyl glycoside in the composition is in a range of about 0.01% (w/v) to about 1% (w/v). In some embodiments, the amount of alkyl glycoside in the composition is in a range of about 0.05% (w/v) to about 0.5% (w/v), or about 0.125% (w/v) to about 0.5% (w/v).

[058] In some embodiments, the composition is in a pharmaceutically-acceptable spray formulation, and further comprising administering the composition to one or more nasal mucosal membranes of the patient. In some embodiments, the therapeutically effective amount is from about 1 mg to about 20 mg of the benzodiazepine. In some embodiments, the pharmaceutical composition is in a pharmaceutically-acceptable spray formulation having volume from about 10 μL to 200 μL.

[059] In some embodiments, the administration of the composition comprises spraying at least a portion of the therapeutically effective amount of the composition into at least one nostril. In some embodiments, the administration of the composition comprises spraying at least a portion of the therapeutically effective amount of the composition into each nostril. In some embodiments, the administration of the composition comprises spraying a first quantity of the composition into the first nostril, spraying a second quantity of the composition into a second nostril, and optionally after a pre-selected time delay, spraying a third quantity of the composition into the first nostril. Some embodiments further comprise, optionally after a pre-selected time delay, administering at least a fourth quantity of the composition to the second nostril.

[060] In some embodiments, the administration of the composition begins at any time before or after onset of symptoms of a disorder which may be treatable with the composition.

Definitions

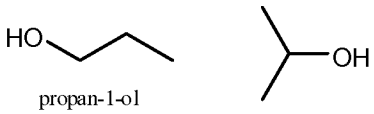
[061] As used herein the phrase "therapeutically effective amount" (or more simply "effective amount") includes an amount sufficient to provide a specific therapeutic response for which the drug is administered to a patient in need of particular treatment. The skilled clinician will recognize that the therapeutically effective amount of drug will depend upon the patient, the indication and the particular drug administered.

[062] As used herein, the modifier "about" is intended to have its regularly recognized meaning of approximately. In some embodiments, the term may be more precisely interpreted as meaning within a particular percentage of the modified value, e.g. "about" may in some embodiments mean ± 20%, ± 10%, ± 5%, ± 2%, or ± 1% or less.

[063] As used herein, the phrase "analogs or derivatives" includes molecules that differ from one another molecule due to one or more atoms or functional groups having been replaced with a different atom or

functional group. This may result in molecules with similar chemical formulas but different chemical and/or biological properties.

[064] As used herein, the term, "isomer" includes molecules with identical chemical formulas, but between which the arrangement of the molecules may vary. These varying arrangements may result in molecules with identical chemical formulas but different chemical properties. By way of non-limiting example, propanol has the chemical formula C_3H_7OH. It may be found as propan-1-ol, wherein the –OH is found attached to an end carbon. Alternatively, it may be found as propan-2-ol, wherein the –OH is found attached to the second carbon.



propan-1-ol propan-2-ol

[065] As used herein, the term "seizure" includes commonly recognized types of seizures, including absence seizures, myoclonic seizures, clonic seizures, tonic seizures, tonic-clonic seizures, and atonic seizures. Often seizures, particularly severe tonic or tonic-clonic seizures, will be presaged by one or more aura that will be familiar to the patient or those familiar with the patient. Each patient will generally experience a different type of aura, which is unique to the patient; however auras may be classified as audible, visual, olfactory or tactile sensations that usually, or at least often, precedes a patient's experiencing a seizure. (Not all patients who suffer seizures experience aura; however aura are not uncommon amongst those who suffer the worst type of seizures, especially tonic-clonic seizures.)

[066] As used herein, the term "prevention" refers to a forestalling, including temporary forestalling, of the onset of a disorder. In the case of seizures, this can occur either with or without the benefit of a warning aura.

[067] As used herein, the term "treatment" refers to a reduction in the intensity and/or duration of a disorder, or similar effects. The term also encompasses the side-effects of such a "treatment."

[068] As used herein, unless otherwise qualified, "a" and "an" can mean one or more.

[069] As used herein, the term "comprising" in all its variants, is a transitional phrase used in a claim to indicate that the invention includes or contains, but is not limited to, the specifically recited claim elements.

[070] As used herein, the phrase "consisting essentially of" is a transitional phrase used in a claim to indicate that the a following list of ingredients, parts or process steps must be present in the claimed composition, machine or process, but that the claim is open to unlisted ingredients, parts or process steps that do not materially affect the basic and novel properties of the invention.

[071] As used herein, the term "consisting of" is a transitional phrase used in a claim to indicate that the claimed invention includes only those elements set forth in the claim.

Benzodiazepine Drugs

[072] In the context of the present invention, the term "benzodiazepine drug" includes any therapeutically effective benzodiazepine compound, or pharmaceutically acceptable salt, or combinations thereof. In some

embodiments, benzodiazepine comprises a member of the group consisting of alprazolam, diazepam, flurazepam, lorazepam, medazepam, mexazolam, midazolam, temazepam and pharmaceutically acceptable salts and combinations thereof.

[073] It should be recognized by those of skill in the art that additional benzodiazepine compounds that have heretofore been considered to have marginal or little therapeutic benefit, either because of low bioavailability, poor pharmacokinetic properties or poor pharmacodynamic properties, may find use through the present invention, which can provide for improved bioavailability of benzodiazepine drugs, delivery of higher concentrations of benzodiazepine drugs via the nasal route, faster attainment of therapeutic levels of benzodiazepine in the blood plasma, avoidance of the liver portal vein and concomitant avoidance of first pass effects and/or faster presentation of benzodiazepine drug to the brain.

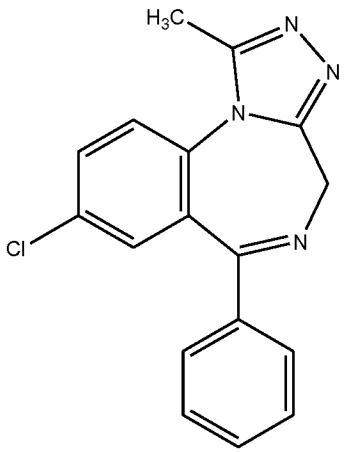
[074] For example, most benzodiazepines are so slightly soluble in water that a therapeutically effective amount cannot be dissolved in a volume of aqueous solvent that is amenable to application to a mucosal membrane. By use of the present carrier system, which in some embodiments, provides an improved ability to dissolve benzodiazepine drugs, the present invention allows benzodiazepine drugs to be administered to one or more mucosal membranes, including to nasal mucosal membranes. This can allow one to administer the drug without hospitalization or unnecessary discomfort. Additionally, in some embodiments of the present invention, such as nasal administration, the digestive system largely may be bypassed. This latter improvement can yield improved bioavailability, faster attainment of therapeutic levels of benzodiazepine in the blood plasma, avoidance of the liver portal vein, and/or concomitant avoidance of first pass effects.

[075] Nasal administration of the composition can result in faster presentation of the one or more benzodiazepine drugs to the brain due to the close proximity of the membranes and the brain. A seizing patient, for example, suffers from rigid muscles and uncontrollable movement. This can make oral and/or intravenous administration difficult or inconvenient. However, the nasal passageways remain open and easily accessible, and therefore is a useful route of administration for of the present invention.

[076] In some embodiments, the pharmaceutical composition is used as defined in the claims to treat a patient suffering from a disorder that is amenable to treatment or prevention with an effective amount of the one or more benzodiazepine drugs. By way of non-limiting example such disorders can include: insomnia, anxiety, seizures, muscle spasms and rigidity, and the symptoms of drug withdrawal.

[077] In some embodiments, the one or more benzodiazepine drugs, are used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure.

[078] **Alprazolam** (8-chloro-6-phenyl-1-methyl-4H-1,2,4-triazolo[4,3-a][1,4]benzodiazepine).



[079] Alprazolam is a benzodiazepine drug having sedative, tranquilizing and muscle relaxing properties. It is classified as an anxiolytic. Alprazolam has also been shown to be useful in the treatment of panic disorder. The dosage of alprazolam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.5 to about 4, preferably about 1 to about 2 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Alprazolam may be manufactured using the process disclosed in United States patent 3,987,052.

[080] In some embodiments, alprazolam is used alone or in combination with other drugs to provide an anxiolytic effect, an anticonvulsant effect, a sedative effect, a skeletal muscle relaxant effect, an amnesic effect or combinations of the foregoing effects.

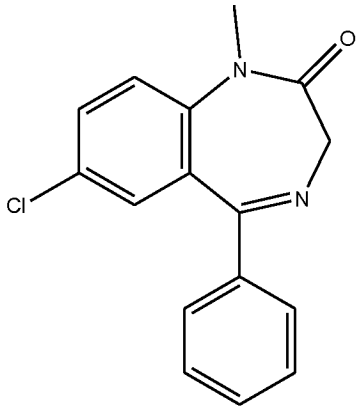
[081] In some embodiments, alprazolam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Alprazolam may be administered by the patient or other person (such as a healthcare professional) while the patient is in a non-seizing state to protect against seizure. Even where protection against seizure is not absolute, administration of alprazolam may reduce or ameliorate the intensity of seizure and/or reduce or ameliorate the frequency of seizure. In some embodiments, administration of alprazolam may prevent occurrence of seizure. In some embodiments, especially where the patient is prone to experiencing serial seizures or *status epilepticus*, administration of alprazolam may aid in interrupting the seizure cycle and may thus prevent the re-occurrence of seizure. In addition to the benzodiazepines (such as diazepam), other anti-convulsant drugs may be combined with alprazolam to provide an anticonvulsant or synergistic anticonvulsant effect.

[082] Alprazolam may also be administered by another person (*e.g.* an acquaintance or associate, a family member or a health care professional) to the patient while the patient is in a state of seizure. Thus, one of the advantages of the formulations for use according to the present invention is the ability to administer them in an acute therapeutic environment to treat the seizure victim, for example, nasally. Among the beneficial therapeutic effects that may be imparted by acute dosing of benzodiazepine anticonvulsants, such as nasal dosing, are: reduction in the severity of the seizure (*e.g.* general relaxation of the muscles, reduction in seizure-induced anxiety experienced by the patient and a general impartation of a feeling of well-being to the

patient), reduction in the duration of the seizure, reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between the current seizure and the next seizure. Thus, the alprazolam formulations of the invention, and in particular nasal formulations, provide fast onset of therapeutic benefit – in some instances less than about 30 minutes, less than about 15 minutes, less than about 10 minutes, and in some cases less than about 5 minutes. The alprazolam formulations of the invention, and in particular nasal formulations, also provide convenient administration of a therapeutically beneficial drug to a patient that does not require intravenous drug administration or rectal drug administration.

[083] Often seizures, particularly severe tonic or tonic-clonic seizures, will be presaged by one or more aura events that will be familiar to the patient or those familiar with the patient. These auras are practically *sui generis* for each patient, but may be classified as audible, visual, olfactory or tactile sensations that usually, or typically, precedes a patient's experiencing a seizure. In some embodiments of the invention, the method includes prompt administration of a preparation of a benzodiazepine drug according to the invention during the aura. In some embodiments, such intra-aural administration of benzodiazepine drug, for example by nasal administration, will prevent or at least ameliorate the effects (intensity, duration or both) of the impending seizure. Thus, in the context of this invention, prevention of seizure refers to a temporary forestalling of the onset of seizure, either with or without the benefit of a warning aura.

[084] **Diazepam** (7-chloro-1-methyl-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one)



[085] Diazepam is a benzodiazepine drug having sedative, tranquilizing and muscle relaxing properties. It is classified as an anxiolytic and skeletal muscle relaxant. It possesses anxiolytic, anticonvulsant, sedative, skeletal muscle relaxant and amnesic properties. The dosage of diazepam may vary by indication, however it is expected that a therapeutic dose will be in the range of about 1 to about 20, preferably about 2 to about 10 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Diazepam may be manufactured using the process disclosed in one of United States patents 3,371,085; 3,109,843; 3,136,815 or 3,102,116.

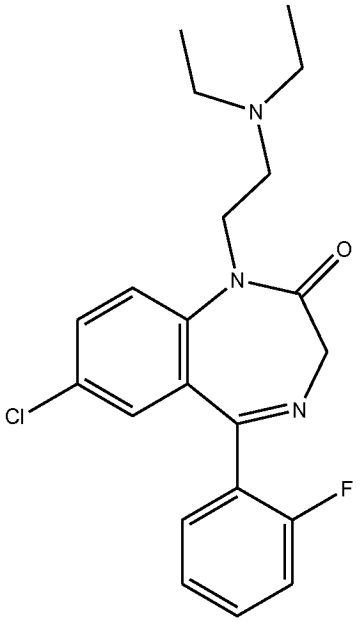
[086] In some embodiments, diazepam is used alone or in combination with other drugs to provide an anxiolytic effect, an anticonvulsant effect, a sedative effect, a skeletal muscle relaxant effect, an amnesic effect or combinations of the foregoing effects.

[087] In some embodiments, diazepam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Diazepam may be administered by the patient or other person (such as a healthcare professional) while the patient is in a non-seizing state to protect against seizure. Even where protection against seizure is not absolute, administration of diazepam may reduce or ameliorate the intensity of seizure and/or reduce or ameliorate the frequency of seizure. In some embodiments, administration of diazepam may prevent occurrence of seizure. In some embodiments, especially where the patient is prone to experiencing serial seizures or status epilepticus, administration of diazepam may aid in interrupting the seizure cycle and may thus prevent the re-occurrence of seizure. In addition to the benzodiazepines (such as diazepam), other anti-convulsant drugs may be combined with diazepam to provide a synergistic anticonvulsant effect.

[088] Diazepam may also be administered by another person (*e.g.* an acquaintance or associate, a family member or a health care professional) to the patient while the patient is in a state of seizure. Thus, one of the advantages of the formulations for use according to the present invention is the ability to administer them in an acute therapeutic environment to treat the seizure victim, for example, nasally. Among the beneficial therapeutic effects that may be imparted by acute dosing of benzodiazepine anticonvulsants, such as nasal dosing, are: reduction in the severity of the seizure (*e.g.* general relaxation of the muscles, reduction in seizure-induced anxiety experienced by the patient and a general impartation of a feeling of well-being to the patient), reduction in the duration of the seizure, reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between the current seizure and the next seizure. Thus, the diazepam formulations of the invention, and in particular nasal formulations, provide fast onset of therapeutic benefit – in some instances less than about 30 minutes, less than about 15 minutes, less than about 10 minutes, and in some cases less than about 5 minutes. The diazepam formulations of the invention, and in particular nasal formulations, also provide convenient administration of a therapeutically beneficial drug to a patient that does not require intravenous drug administration or rectal drug administration.

[089] Often seizures, particularly severe tonic or tonic-clonic seizures, will be presaged by one or more aura events that will be familiar to the patient or those familiar with the patient. These auras are practically *sui generis* for each patient, but may be classified as audible, visual, olfactory or tactile sensations that usually, or typically, precedes a patient's experiencing a seizure. In some embodiments of the invention, the method includes prompt administration of a preparation of a benzodiazepine drug according to the invention during the aura. In some embodiments, such intra-aural administration of benzodiazepine drug, for example by nasal administration, will prevent or at least ameliorate the effects (intensity, duration or both) of the impending seizure. Thus, in the context of this invention, prevention of seizure refers to a temporary forestalling of the onset of seizure, either with or without the benefit of a warning aura.

[090] **Flurazepam** (7-chloro-5-(2-flurophenyl)-2,3-dihydro-1-(2-(diethylamino)ethyl)-1H-1,4-benzodiazepin-2-one)



[091] Flurazepam is a benzodiazepine drug having sedative (especially soporific and hypnotic), anxiolytic, anticonvulsant and muscle relaxing properties. It is classified as an sedative, hypnotic. Flurazepam has been shown to be useful in the treatment of insomnia. The dosage of flurazepam varies by indication, however it is expected that a therapeutic dose will be in the range of about 5 to 40, preferably about 20 to about 35 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Flurazepam may be manufactured using the process disclosed in United States patent 3,567,710 or 3,299,053.

[092] In some embodiments, flurazepam is used alone or in combination with other drugs to provide an anxiolytic effect, an anticonvulsant effect, a sedative effect, a skeletal muscle relaxant effect, an amnesic effect or combinations of the foregoing effects.

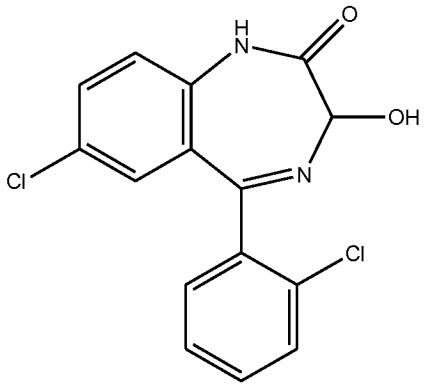
[093] In some embodiments, flurazepam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Flurazepam may be administered by the patient or other person (such as a healthcare professional) while the patient is in a non-seizing state to protect against seizure. Even where protection against seizure is not absolute, administration of flurazepam may reduce or ameliorate the intensity of seizure and/or reduce or ameliorate the frequency of seizure. In some embodiments, administration of flurazepam may prevent occurrence of seizure. In some embodiments, especially where the patient is prone to experiencing serial seizures or status epilepticus, administration of flurazepam may aid in interrupting the seizure cycle and may thus prevent the re-occurrence of seizure. In addition to the benzodiazepines (such as diazepam), other anti-convulsant drugs may be combined with flurazepam to provide a synergistic anticonvulsant effect.

[094] Flurazepam may also be administered by another person (*e.g.* an acquaintance or associate, a family member or a health care professional) to the patient while the patient is in a state of seizure. Thus, one of the advantages of the formulations for use according to the present invention is the ability to administer them in

an acute therapeutic environment to treat the seizure victim, for example, nasally. Among the beneficial therapeutic effects that may be imparted by acute dosing of benzodiazepine anticonvulsants, such as nasal dosing, are: reduction in the severity of the seizure (*e.g.* general relaxation of the muscles, reduction in seizure-induced anxiety experienced by the patient and a general impartation of a feeling of well-being to the patient), reduction in the duration of the seizure, reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between the current seizure and the next seizure. Thus, the flurazepam formulations of the invention, and in particular nasal formulations, provide fast onset of therapeutic benefit – in some instances less than about 30 minutes, less than about 15 minutes, less than about 10 minutes, and in some cases less than about 5 minutes. The flurazepam formulations of the invention, and in particular nasal formulations, also provide convenient administration of a therapeutically beneficial drug to a patient that does not require intravenous drug administration or rectal drug administration.

[095] Often seizures, particularly severe tonic or tonic-clonic seizures, will be presaged by one or more aura events that will be familiar to the patient or those familiar with the patient. These auras are practically *sui generis* for each patient, but may be classified as audible, visual, olfactory or tactile sensations that usually, or typically, precedes a patient's experiencing a seizure. In some embodiments of the invention, the method includes prompt administration of a preparation of a benzodiazepine drug according to the invention during the aura. In some embodiments, such intra-aural administration of benzodiazepine drug, for example by nasal administration, will prevent or at least ameliorate the effects (intensity, duration or both) of the impending seizure. Thus, in the context of this invention, prevention of seizure refers to a temporary forestalling of the onset of seizure, either with or without the benefit of a warning aura.

[096] **Lorazepam** (7-chloro-5-(2-chlorophenyl)-3-hydroxy-1,3-dihydro-2H-1,4-benzodiazepin-2-one)



[097] Lorazepam is a benzodiazepine drug having sedative, tranquilizing, anticonvulsant, amnesic and muscle relaxing properties. It is classified as an anxiolytic. Lorazepam has also been shown to be useful in the treatment of nausea. The dosage of lorazepam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.1 to about 10, preferably about 0.2 to about 1 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Lorazepam may be manufactured using the process disclosed in United States patent 3,296,249.

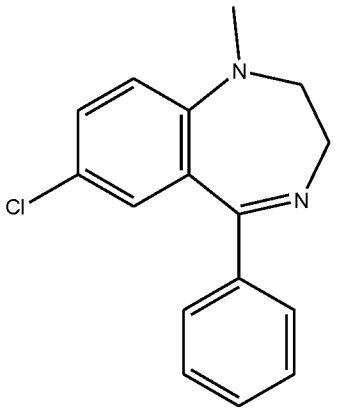
[098] In some embodiments, lorazepam is used alone or in combination with other drugs to provide an anxiolytic effect, an anticonvulsant effect, a sedative effect, a skeletal muscle relaxant effect, an amnesic effect or combinations of the foregoing effects.

[099] In some embodiments, lorazepam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Lorazepam may be administered by the patient or other person (such as a healthcare professional) while the patient is in a non-seizing state to protect against seizure. Even where protection against seizure is not absolute, administration of lorazepam may reduce or ameliorate the intensity of seizure and/or reduce or ameliorate the frequency of seizure. In some embodiments, administration of lorazepam may prevent occurrence of seizure. In some embodiments, especially where the patient is prone to experiencing serial seizures or status epilepticus, administration of lorazepam may aid in interrupting the seizure cycle and may thus prevent the re-occurrence of seizure. In addition to the benzodiazepines (such as diazepam), other anti-convulsant drugs may be combined with lorazepam to provide a synergistic anticonvulsant effect.

[0100] Lorazepam may also be administered by another person (*e.g.* an acquaintance or associate, a family member or a health care professional) to the patient while the patient is in a state of seizure. Thus, one of the advantages of the formulations for use according to the present invention is the ability to administer them in an acute therapeutic environment to treat the seizure victim, for example, nasally. Among the beneficial therapeutic effects that may be imparted by acute dosing of benzodiazepine anticonvulsants, such as nasal dosing, are: reduction in the severity of the seizure (*e.g.* general relaxation of the muscles, reduction in seizure-induced anxiety experienced by the patient and a general impartation of a feeling of well-being to the patient), reduction in the duration of the seizure, reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between the current seizure and the next seizure. Thus, the lorazepam formulations of the invention, and in particular nasal formulations, provide fast onset of therapeutic benefit – in some instances less than about 30 minutes, less than about 15 minutes, less than about 10 minutes, and in some cases less than about 5 minutes. The lorazepam formulations of the invention, and in particular nasal formulations, also provide convenient administration of a therapeutically beneficial drug to a patient that does not require intravenous drug administration or rectal drug administration.

[0101] Often seizures, particularly severe tonic or tonic-clonic seizures, will be presaged by one or more aura events that will be familiar to the patient or those familiar with the patient. These auras are practically *sui generis* for each patient, but may be classified as audible, visual, olfactory or tactile sensations that usually, or typically, precedes a patient's experiencing a seizure. In some embodiments of the invention, the method includes prompt administration of a preparation of a benzodiazepine drug according to the invention during the aura. In some embodiments, such intra-aural administration of benzodiazepine drug, for example by nasal administration, will prevent or at least ameliorate the effects (intensity, duration or both) of the impending seizure. Thus, in the context of this invention, prevention of seizure refers to a temporary forestalling of the onset of seizure, either with or without the benefit of a warning aura.

[0102] **Medazepam** ((7-chloro-1-methyl-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepine)



[0103] Medazepam is a benzodiazepine drug having sedative, tranquilizing, anticonvulsant, amnesic and muscle relaxing properties. It is classified as an anxiolytic. Medazepam has also been shown to be useful in the treatment of nausea. The dosage of medazepam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.1 to about 10, preferably about 0.2 to about 1 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Medazepam may be manufactured using the process disclosed in United States patent 3,243,427.

[0104] In some embodiments, medazepam is used alone or in combination with other drugs to provide an anxiolytic effect, an anticonvulsant effect, a sedative effect, a skeletal muscle relaxant effect, an amnesic effect or combinations of the foregoing effects.

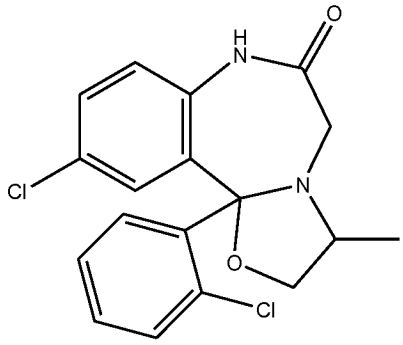
[0105] In some embodiments, medazepam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Medazepam may be administered by the patient or other person (such as a healthcare professional) while the patient is in a non-seizing state to protect against seizure. Even where protection against seizure is not absolute, administration of medazepam may reduce or ameliorate the intensity of seizure and/or reduce or ameliorate the frequency of seizure. In some embodiments, administration of medazepam may prevent occurrence of seizure. In some embodiments, especially where the patient is prone to experiencing serial seizures or status epilepticus, administration of medazepam may aid in interrupting the seizure cycle and may thus prevent the re-occurrence of seizure. In addition to the benzodiazepines (such as diazepam), other anti-convulsant drugs may be combined with medazepam to provide a synergistic anticonvulsant effect.

[0106] Medazepam may also be administered by another person (*e.g.* an acquaintance or associate, a family member or a health care professional) to the patient while the patient is in a state of seizure. Thus, one of the advantages of the formulations for use according to the present invention is the ability to administer them in an acute therapeutic environment to treat the seizure victim, for example, nasally. Among the beneficial therapeutic effects that may be imparted by acute dosing of benzodiazepine anticonvulsants, such as nasal dosing, are: reduction in the severity of the seizure (*e.g.* general relaxation of the muscles, reduction in seizure-induced anxiety experienced by the patient and a general impartation of a feeling of well-being to the

patient), reduction in the duration of the seizure, reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between the current seizure and the next seizure. Thus, the medazepam formulations of the invention, and in particular nasal formulations, provide fast onset of therapeutic benefit – in some instances less than about 30 minutes, less than about 15 minutes, less than about 10 minutes, and in some cases less than about 5 minutes. The medazepam formulations of the invention, and in particular nasal formulations, also provide convenient administration of a therapeutically beneficial drug to a patient that does not require intravenous drug administration or rectal drug administration.

[0107] Often seizures, particularly severe tonic or tonic-clonic seizures, will be presaged by one or more aura events that will be familiar to the patient or those familiar with the patient. These auras are practically *sui generis* for each patient, but may be classified as audible, visual, olfactory or tactile sensations that usually, or typically, precedes a patient's experiencing a seizure. In some embodiments of the invention, the method includes prompt administration of a preparation of a benzodiazepine drug according to the invention during the aura. In some embodiments, such intra-aural administration of benzodiazepine drug, for example by nasal administration, will prevent or at least ameliorate the effects (intensity, duration or both) of the impending seizure. Thus, in the context of this invention, prevention of seizure refers to a temporary forestalling of the onset of seizure, either with or without the benefit of a warning aura.

[0108] **Mexazolam** (10-Chloro-11b-(2-chlorophenyl)-1,3,7,11b-tetrahydro-3-methyloxazolo[3,2-d][1,4]benzodiazepin-6(5H)-one)



[0109] Mexazolam is a benzodiazepine drug having sedative, tranquilizing, anticonvulsant, amnesic and muscle relaxing properties. It is classified as an anxiolytic. Mexazolam has also been shown to be useful in the treatment of nausea. The dosage of mexazolam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.1 to about 10, preferably about 0.2 to about 1 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Mexazolam may be manufactured using the process disclosed in United States patent 3,722,371.

[0110] In some embodiments, mexazolam is used alone or in combination with other drugs to provide an anxiolytic effect, an anticonvulsant effect, a sedative effect, a skeletal muscle relaxant effect, an amnesic effect or combinations of the foregoing effects.

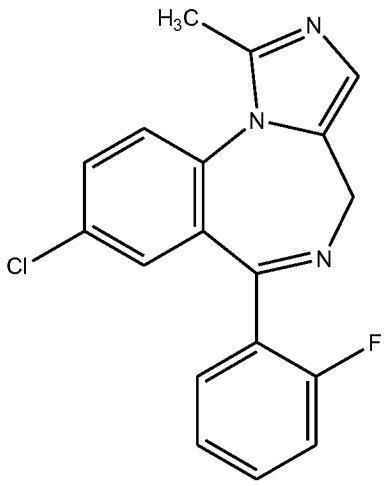
[0111] In some embodiments, mexazolam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Mexazolam may be administered

by the patient or other person (such as a healthcare professional) while the patient is in a non-seizing state to protect against seizure. Even where protection against seizure is not absolute, administration of mexazolam may reduce or ameliorate the intensity of seizure and/or reduce or ameliorate the frequency of seizure. In some embodiments, administration of mexazolam may prevent occurrence of seizure. In some embodiments, especially where the patient is prone to experiencing serial seizures or status epilepticus, administration of mexazolam may aid in interrupting the seizure cycle and may thus prevent the re-occurrence of seizure. In addition to the benzodiazepines (such as diazepam), other anti-convulsant drugs may be combined with mexazolam to provide a synergistic anticonvulsant effect.

[0112] Mexazolam may also be administered by another person (*e.g.* an acquaintance or associate, a family member or a health care professional) to the patient while the patient is in a state of seizure. Thus, one of the advantages of the formulations for use according to the present invention is the ability to administer them in an acute therapeutic environment to treat the seizure victim, for example, nasally. Among the beneficial therapeutic effects that may be imparted by acute dosing of benzodiazepine anticonvulsants, such as nasal dosing, are: reduction in the severity of the seizure (*e.g.* general relaxation of the muscles, reduction in seizure-induced anxiety experienced by the patient and a general impartation of a feeling of well-being to the patient), reduction in the duration of the seizure, reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between the current seizure and the next seizure. Thus, the mexazolam formulations of the invention, and in particular nasal formulations, provide fast onset of therapeutic benefit – in some instances less than about 30 minutes, less than about 15 minutes, less than about 10 minutes, and in some cases less than about 5 minutes. The mexazolam formulations of the invention, and in particular nasal formulations, also provide convenient administration of a therapeutically beneficial drug to a patient that does not require intravenous drug administration or rectal drug administration.

[0113] Often seizures, particularly severe tonic or tonic-clonic seizures, will be presaged by one or more aura events that will be familiar to the patient or those familiar with the patient. These auras are practically *sui generis* for each patient, but may be classified as audible, visual, olfactory or tactile sensations that usually, or typically, precedes a patient's experiencing a seizure. In some embodiments of the invention, the method includes prompt administration of a preparation of a benzodiazepine drug according to the invention during the aura. In some embodiments, such intra-aural administration of benzodiazepine drug, for example by nasal administration, will prevent or at least ameliorate the effects (intensity, duration or both) of the impending seizure. Thus, in the context of this invention, prevention of seizure refers to a temporary forestalling of the onset of seizure, either with or without the benefit of a warning aura.

[0114] **Midazolam** (8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo(1,5-a)benzodiazepine).



[0115] Midazolam is a tricyclic benzodiazepine having anxiolytic, amnesic, hypnotic, anticonvulsant, skeletal muscle relaxant and sedative properties. Midazolam is considered soluble in water at a pH lower than about 4, but is relatively insoluble in most aqueous solutions at neutral pH (e.g. about 6 to 8). Thus it is desirable in some embodiments for aqueous nasal preparations of midazolam to have a pH above about 5.5, preferably above about 6.0, or above about 6.5. In some preferred embodiments, the pH is between about 6 and 9, between about 6 and 8. It is considered that preparations of midazolam are particularly suitable for nasal administration as the lipid-soluble (at approximately neutral pH) midazolam is rapidly absorbed across nasal mucosa, leading to efficient uptake of midazolam. It is further considered that midazolam may be formulated in a non-aqueous delivery vehicle, such as is known in the aerosol administration art, such as hydrofluorocarbon propellants, hydrocarbon propellants, etc.

[0116] The dosage of midazolam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.1 to about 20, preferably about 0.2 to about 10 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Midazolam may be manufactured using the process disclosed in one of United States patents 4,280,957 or 5,831,089.

[0117] In some embodiments, midazolam is used alone or in combination with other drugs to provide an anxiolytic effect, an anticonvulsant effect, a sedative effect, a skeletal muscle relaxant effect, an amnesic effect or combinations of the foregoing effects.

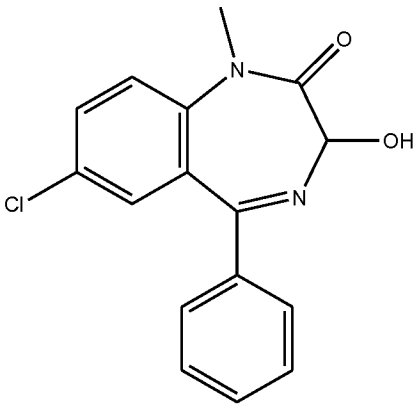
[0118] In some embodiments, midazolam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Midazolam may be administered by the patient or other person (such as a healthcare professional) while the patient is in a non-seizing state to protect against seizure. Even where protection against seizure is not absolute, administration of midazolam may reduce or ameliorate the intensity of seizure and/or reduce or ameliorate the frequency of seizure. In some embodiments, administration of midazolam may prevent occurrence of seizure. In some embodiments, especially where the patient is prone to experiencing serial seizures or status epilepticus, administration of midazolam may aid in interrupting the seizure cycle and may thus prevent the re-occurrence of seizure. In

addition to the benzodiazepines (such as diazepam), other anti-convulsant drugs may be combined with midazolam to provide a synergistic anticonvulsant effect.

[0119] Midazolam may also be administered by another person (*e.g.* an acquaintance or associate, a family member or a health care professional) to the patient while the patient is in a state of seizure. Thus, one of the advantages of the formulations for use according to the present invention is the ability to administer them in an acute therapeutic environment to treat the seizure victim, for example, nasally. Among the beneficial therapeutic effects that may be imparted by acute dosing of benzodiazepine anticonvulsants, such as nasal dosing, are: reduction in the severity of the seizure (*e.g.* general relaxation of the muscles, reduction in seizure-induced anxiety experienced by the patient and a general impartation of a feeling of well-being to the patient), reduction in the duration of the seizure, reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between the current seizure and the next seizure. Thus, the midazolam formulations of the invention, and in particular nasal formulations, provide fast onset of therapeutic benefit – in some instances less than about 30 minutes, less than about 15 minutes, less than about 10 minutes, and in some cases less than about 5 minutes. The midazolam formulations of the invention, and in particular nasal formulations, also provide convenient administration of a therapeutically beneficial drug to a patient that does not require intravenous drug administration or rectal drug administration.

[0120] Often seizures, particularly severe tonic or tonic-clonic seizures, will be presaged by one or more aura events that will be familiar to the patient or those familiar with the patient. These auras are practically *sui generis* for each patient, but may be classified as audible, visual, olfactory or tactile sensations that usually, or typically, precedes a patient's experiencing a seizure. In some embodiments of the invention, the method includes prompt administration of a preparation of a benzodiazepine drug according to the invention during the aura. In some embodiments, such intra-aural administration of benzodiazepine drug, for example by nasal administration, will prevent or at least ameliorate the effects (intensity, duration or both) of the impending seizure. Thus, in the context of this invention, prevention of seizure refers to a temporary forestalling of the onset of seizure, either with or without the benefit of a warning aura.

[0121] **Temazepam** (7-chloro-1-methyl-5-phenyl-3-hydroxy-1,3-dihydro-2H-1,4-benzodiazepin-2-one)



[0122] Temazepam is a benzodiazepine drug having sedative, tranquilizing, anticonvulsant, amnesic and muscle relaxing properties. It is classified as an anxiolytic. Temazepam has also been shown to be useful in

the treatment of nausea. The dosage of temazepam varies by indication, however it is expected that a therapeutic dose will be in the range of about 1 to about 50, preferably about 5 to about 30 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Temazepam may be manufactured using the process disclosed in United States patent 3,340,253 or 3,374,225.

[0123] In some embodiments, temazepam is used alone or in combination with other drugs to provide an anxiolytic effect, an anticonvulsant effect, a sedative effect, a skeletal muscle relaxant effect, an amnesic effect or combinations of the foregoing effects.

[0124] In some embodiments, temazepam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Temazepam may be administered by the patient or other person (such as a healthcare professional) while the patient is in a non-seizing state to protect against seizure. Even where protection against seizure is not absolute, administration of temazepam may reduce or ameliorate the intensity of seizure and/or reduce or ameliorate the frequency of seizure. In some embodiments, administration of temazepam may prevent occurrence of seizure. In some embodiments, especially where the patient is prone to experiencing serial seizures or status epilepticus, administration of temazepam may aid in interrupting the seizure cycle and may thus prevent the re-occurrence of seizure. In addition to the benzodiazepines (such as diazepam), other anti-convulsant drugs may be combined with temazepam to provide a synergistic anticonvulsant effect.

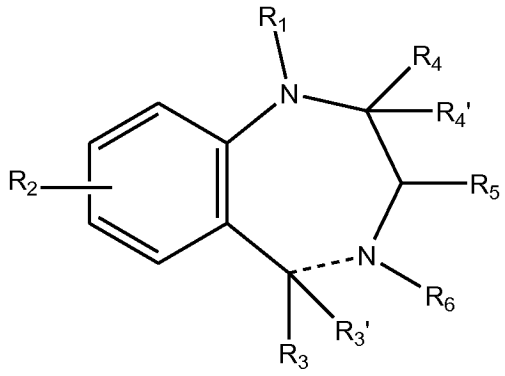
[0125] Temazepam may also be administered by another person (*e.g.* an acquaintance or associate, a family member or a health care professional) to the patient while the patient is in a state of seizure. Thus, one of the advantages of the formulations for use according to the present invention is the ability to administer them in an acute therapeutic environment to treat the seizure victim, for example, nasally. Among the beneficial therapeutic effects that may be imparted by acute dosing of benzodiazepine anticonvulsants, such as nasal dosing, are: reduction in the severity of the seizure (*e.g.* general relaxation of the muscles, reduction in seizure-induced anxiety experienced by the patient and a general impartation of a feeling of well-being to the patient), reduction in the duration of the seizure, reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between the current seizure and the next seizure. Thus, the temazepam formulations of the invention, and in particular nasal formulations, provide fast onset of therapeutic benefit – in some instances less than about 30 minutes, less than about 15 minutes, less than about 10 minutes, and in some cases less than about 5 minutes. The temazepam formulations of the invention, and in particular nasal formulations, also provide convenient administration of a therapeutically beneficial drug to a patient that does not require intravenous drug administration or rectal drug administration.

[0126] Often seizures, particularly severe tonic or tonic-clonic seizures, will be presaged by one or more aura events that will be familiar to the patient or those familiar with the patient. These auras are practically *sui generis* for each patient, but may be classified as audible, visual, olfactory or tactile sensations that usually, or typically, precedes a patient's experiencing a seizure. In some embodiments of the invention, the method includes prompt administration of a preparation of a benzodiazepine drug according to the invention during

the aura. In some embodiments, such intra-aural administration of benzodiazepine drug, for example by nasal administration, will prevent or at least ameliorate the effects (intensity, duration or both) of the impending seizure. Thus, in the context of this invention, prevention of seizure refers to a temporary forestalling of the onset of seizure, either with or without the benefit of a warning aura.

Pharmaceutically Acceptable Salts

[0127] Benzodiazepines have the generally basic structure of formula I:



Formula I

wherein R_1-R_5 are substituents. In particular embodiments, R_1 is an optionally substituted alkyl or forms a ring with R_4, R_2 is a halogen (e.g. Cl, Br), R_3 is optionally substituted aryl (e.g. 2-Chloro or 2-Fluorophenyl), R_5 is H or OH, R_4 and R_4' together form a carbonyl (C=O) with the carbon to which they are attached or R_4 and R_1 form an optionally substituted heterocyclic ring with the diazepam ring atoms to which they are respectively attached; R_3' and R_6 together form a double bond or may be combined to form an optionally substituted heterocyclic ring along with the diazepam ring atoms to which they are respectively attached. Such basic compounds may form acid addition salts with pharmaceutically acceptable acids, such as pharmaceutically acceptable mineral acids and pharmaceutically acceptable organic acids.

[0128] Pharmaceutically acceptable mineral acids include HCl, H_2SO_4, H_2SO_3, H_3PO_4, H_3PO_3, and others that will be recognized by those of skill in the art. Pharmaceutically acceptable organic acids include acetic acid, benzoic acid, tartaric acid, citric acid, oxalic acid, maleic acid, malonic acid, etc. Thus, in some embodiments, the pharmaceutically acceptable acid may be selected from the group consisting of: 1-hydroxy-2-naphthoic acid, 2,2-dichloroacetic acid, 2-hydroxyethanesulfonic acid, 2-oxoglutaric acid, 4-acetamidobenzoic acid, 4-aminosalicylic acid, acetic acid, adipic acidascorbic acid (L), aspartic acid (L), benzenesulfonic acid, benzoic acid, camphoric acid (+), camphor-10-sulfonic acid (+), capric acid (decanoic acid), caproic acid (hexanoic acid), caprylic acid (octanoic acid), carbonic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, formic acidfumaric acid, galactaric acid, gentisic acid, glucoheptonic acid (D), gluconic acid (D), glucuronic acid (D), glutamic acid,

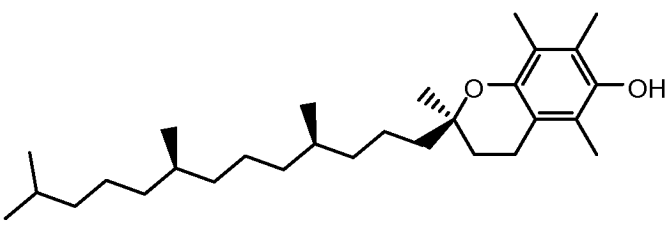
glutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, hydrobromic acid, hydrochloric acid, isobutyric acid, lactic acid (DL), lactobionic acid, lauric acid, maleic acid, malic acid (- L), malonic acid, mandelic acid (DL), methanesulfonic acid, benzenesulfonic acid (besylic acid), naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, nicotinic acid, nitric acid, oleic acid, oxalic acid, palmitic acid, pamoic acid, phosphoric acid, proprionic acid, pyroglutamic acid (- L), salicylic acid, sebacic acid, stearic acid, succinic acid, sulfuric acid, tartaric acid (+ L), thiocyanic acid, toluenesulfonic acid (p) and undecylenic acid. Other pharmaceutically acceptable acids may be pharmaceutically acceptable acidic (anionic) polymers or pharmaceutically acceptable amphoteric polymers. One skilled in the art will recognize that other basic active pharmaceutical ingredients may be combined with the foregoing acids to produce acid addition salts. Likewise the person skilled in the art will recognize that in some embodiments it may be advantageous that some or all of the added acid be an active pharmaceutical ingredient in its own right.

[0129] In some embodiments, the invention provides nasal compositions comprising one or more acidic pharmaceutically active ingredients. It is considered well within the ordinary skill in the art to determine which of the compounds set for the above are acidic. Such compounds may be prepared as base addition salts, e.g. by the addition of one or more mineral bases (e.g. NaOH, KOH, $NaHCO_3$, Na_2CO_3, NH_3) or organic bases. It is considered within the skill in the art to choose a pharmaceutically acceptable base.

[0130] Known benzodiazepine compounds have anxiolytic, anticonvulsant, sedative and/or skeletal muscle relaxant effect. The term "anticonvulsant" includes treatment of seizures, protection against seizure, reduction or amelioration of the intensity of seizure, reduction or amelioration of the frequency of seizure, and/or prevention of the occurrence or re-occurrence of seizure. In this regard, treatment of seizure includes cessation of an ongoing seizure, reduction in the severity of an ongoing seizure, reduction in the duration of an ongoing seizure. Protection against seizure includes forestalling an oncoming seizure.

Carrier System

[0131] Vitamin E is a class of fat soluble methylated phenols. There are at least eight naturally-occurring compounds that comprise this class: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ- tocotrienol, and δ- tocotrienol, all of which may be used in the compositions and methods of the present invention. There are multiple isomers of each of these compounds, all of which may be used in the compositions and methods of the present invention. There are also multiple esters of each of these compounds, including tocophersolan, all of which may be used in the compositions and methods of the present invention. As used herein, Vitamin E refers to any of the natural or synthetic tocopherols, tocotrienols, any isomers thereof, any esters thereof, any analogs or derivatives thereof, or any combinations thereof.



α-tocopherol

[0132] The compounds that comprise Vitamin E are antioxidants. There is also evidence that they can prevent, delay the onset of, or ameliorate the symptoms of heart disease, cancer, cataracts, macular degeneration, glaucoma, Alzheimer's, and Parkinson's disease.

[0133] The inventors have found that Vitamin E can provide an effective carrier for benzodiazepine drugs. In some embodiments, benzodiazepines are soluble, or partially soluble, in Vitamin E. In some embodiments, Vitamin E may be present as microparticles, nanoparticles, or any combination thereof. Furthermore, use of Vitamin E can have the added benefit of either avoiding irritation of sensitive mucosal membranes and/or soothing irritated mucosal membranes.

[0134] Vitamin E is generally classified as hydrophobic, and when used as a carrier may be limited to formulations as an emulsion. However, emulsions can have several drawbacks. For instance, they may be difficult to create and can be highly unstable. Additionally, they can leave an oily film on the surface of the skin. Thus, to avoid the drawbacks of emulsions, some embodiments of the present invention comprise solutions of one or more benzodiazepine drugs in Vitamin E and one or more lower alkyl alcohols or one or more lower alkyl glycols, or any combinations thereof.

[0135] Lower alkyl alcohols are those with six or fewer carbon atoms. Thus, any of ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, or any combinations thereof can be used.

[0136] Lower alkyl glycols are those with six or fewer carbon atoms. Thus, any of ethylene glycol, propylene glycol, butylene glycol, pentylene glycol, any isomers thereof, or any combinations thereof can be used.

Additional Excipients

[0137] In some embodiments, a composition comprises at least one penetration enhancer in addition to a benzodiazepine drug, a natural or synthetic tocopherol or tocotrienol, and an alcohol or glycol. In some embodiments, the penetration enhancer is at least one alkyl glycoside. In some embodiments, the alkyl glycoside refers to any sugar joined to any hydrophobic alkyl, as described in United States patent number 5,661,130. The hydrophobic alkyl can be any suitable length, for example about 9 to about 24 carbons in length, especially about 10 to about 14 carbons in length. The hydrophobic alkyl can be branched and/or partially or wholly unsaturated. The alkyl may be joined to the saccharide core for example through a carbonyl group, whereby an ester group may be formed. A suitable alkyl glycoside will have the characteristics of being nontoxic, nonionic, and capable of increasing the absorption of a benzodiazepine drug when it is administered intranasally as described herein. Exemplary saccharides that may be covalently joined to an alkyl according to the present invention include glucose, maltose, maltotriose, maltotetrose, sucrose and trehalose. Exemplary alkyl glycosides that may be employed include octyl-, nonyl-, decyl-, undecyl-, dodecyl, tridecyl, tetradecyl, pentadecyl, octadecyl α- or β-D-maltoside, -glucoside or sucroside. In some embodiments, the preferred glycosides include maltose, sucrose or glucose linked by glycosidic linkage to an alkyl chain of 9, 10, 12, 14, 16, 18 or 20 carbon atoms. Specific excipients that may be employed in a nasal composition according to the invention include alkylsaccharide is dodecyl maltoside, tetradecyl maltoside, sucrose

dodecanoate, sucrose monostearate, sucrose distearate, and/or combinations of two or more thereof. Alkyl glycosides that are particularly considered useful in embodiments of the invention include those marketed under the name Intravail® by Aegis Therapeutics, LLC, San Diego, CA. Other alkyl glycosides may be selected from those having a hydrophile-lipophile balance (HLB) number of from about 10-20, especially about 11-15. The HLB number may be determined as set forth in the publication US2009/0047347, published on 19 February 2009, the entirety of which, and especially paragraphs [0075]-[0079]. Where present, the amount of alkyl glycoside in the composition is sufficient to enhance the absorption of a benzodiazepine drug administered by the intranasal route. In some embodiments, the amount of alkyl glycoside in the composition is selected so as to enhance absorption of the benzodiazepine drug, while at the same time not significantly irritating the nasal mucosa. In some embodiments, the amount of alkyl glycoside in the composition is in a range of about 0.01% (w/v) to about 1% (w/v). In some embodiments, the amount of alkyl glycoside in the composition is in a range of about 0.05% (w/v) to about 0.5% (w/v), or about 0.125% (w/v) to about 0.5% (w/v).

[0138] The term "penetration enhancer", means any material which acts to increase absorption across the mucosa and/or increases bioavailability. In some embodiments, such materials include mucolytic agents, degradative enzyme inhibitors and compounds which increase permeability of the mucosal cell membranes. Whether a given compound is an "enhancer" can be determined by comparing two formulations comprising a non-associated, small polar molecule as the drug, with or without the enhancer, in an in vivo or good model test and determining whether the uptake of the drug is enhanced to a clinically significant degree. The enhancer should not produce any problems in terms of chronic toxicity because in vivo the enhancer should be non-irritant and/or rapidly metabolized to a normal cell constituent that does not have any significant irritant effect.

[0139] In some embodiments, preferred enhancing materials lysophospholipids, for example lysophosphatidylcholine obtainable from egg or soy lecithin. Other lysophosphatidylcholines that have different acyl groups as well as lyso compounds produced from phosphatidylethanolamines and phosphatidic acid which have similar membrane modifying properties may be used. Acyl carnitines (e.g. palmitoyl-dl-carnitine-chloride) is an alternative. In some embodiments, a suitable concentration is from 0.02 to 20% (w/v).

[0140] In some embodiments, enhancing agents that are appropriate include chelating agents (EGTA, EDTA, alginates), surface active agents (especially non-ionic materials), acyl glycerols, fatty acids and salts, tyloxapol and biological detergents listed in the SIGMA Catalog, 1988, page 316-321. Also agents that modify the membrane fluidity and permeability are appropriate such as enamines (e.g. phenylalanine enamine of ethylacetoacetate), malonates (e.g. diethyleneoxymethylene malonate), salicylates, bile salts and analogues and fusidates. Suitable concentrations are up to 20% (w/v).

[0141] Thus, in some embodiments, the invention provides a pharmaceutical composition for nasal administration comprising: a benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); one or more alkyl glycosides; and one or more alcohols or glycols, or any combinations thereof, in an amount from about

10% to about 70% (w/w), in a pharmaceutically-acceptable formulation for administration to one or more nasal mucosal membranes of a patient. In some embodiments, the alkyl glycoside is an Intravail® brand alkyl glycoside. In some embodiments, the alkyl glycoside is dodecyl maltoside, tetradecyl maltoside, sucrose dodecanoate, sucrose monostearate, sucrose distearate, and/or a combination of two or more thereof. In some embodiments, the alkyl glycoside is dodecyl maltoside. In some embodiments, the alkyl glycoside is tetradecyl maltoside. In some embodiments, the alkyl glycoside is sucrose dodecanoate. In some embodiments, the alkyl glycoside is sucrose monostearate. In some embodiments, the alkyl glycoside is sucrose distearate. In some embodiments, the alkyl glycoside is a combination of two or more of dodecyl maltoside, tetradecyl maltoside, sucrose dodecanoate, sucrose monostearate, or sucrose distearate.

[0142] Thus, in some embodiments, the invention provides a pharmaceutical composition for nasal administration comprising: a benzodiazepine drug, which benzodiazepine drug comprises microparticles, nanoparticles or both, one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); one or more alkyl glycosides; and one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w), in a pharmaceutically-acceptable formulation for administration to one or more nasal mucosal membranes of a patient. In some embodiments, the alkyl glycoside is an Intravail® brand alkyl glycoside. In some embodiments, the alkyl glycoside is dodecyl maltoside, tetradecyl maltoside, sucrose dodecanoate, sucrose monostearate, sucrose distearate, and/or a combination of two or more thereof. In some embodiments, the alkyl glycoside is dodecyl maltoside. In some embodiments, the alkyl glycoside is tetradecyl maltoside. In some embodiments, the alkyl glycoside is sucrose dodecanoate. In some embodiments, the alkyl glycoside is sucrose monostearate. In some embodiments, the alkyl glycoside is sucrose distearate. In some embodiments, the alkyl glycoside is a combination of two or more of dodecyl maltoside, tetradecyl maltoside, sucrose dodecanoate, sucrose monostearate, or sucrose distearate.

Mucosal Membrane Preparations

[0143] Mucosal membrane preparations are generally administered in metered sprays having volumes of less than 250 µL, preferably less than 150 µL, and ideally from 25 to 100 µL. Although not prohibited in this invention, administration of volumes larger than about 300 µL per dose usually exceeds the absorption capacity of the membranes. This results in a large portion of the pharmaceutically-active ingredient being lost.

[0144] The dosage volume of preparations, in particular nasal preparations, preferably ranges from 25 to 100 µL. Volumes in excess of the aforementioned ranges may bypass the sinuses and flow down the back of the throat where the excess is swallowed.

Alprazolam

[0145] The dosage of alprazolam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.5 to about 4, preferably about 1 to about 2 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Alprazolam may be manufactured using the process disclosed in United States patent 3,987,052.

[0146] As a nasal formulation, alprazolam may be administered in 25 to 250 μL metered sprays. In some preferred embodiments, alprazolam is administered in 50 to 150 μL, especially about 100 μL, metered sprays

Diazepam

[0147] The dosage of diazepam may vary by indication, however it is expected that a therapeutic dose will be in the range of about 1 to about 20, preferably about 2 to about 10 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Diazepam may be manufactured using the process disclosed in one of United States patents 3,371,085, 3,109,843, 3,136,815 or 3,102,116.

[0148] As a nasal formulation, diazepam may be administered in 25 to 250 μL metered sprays. In some preferred embodiments, diazepam is administered in 50 to 150 μL, especially about 100 μL, metered sprays.

Flurazepam

[0149] The dosage of flurazepam varies by indication, however it is expected that a therapeutic dose will be in the range of about 5 to 40, preferably about 20 to about 35 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Flurazepam may be manufactured using the process disclosed in United States patent 3,567,710 or 3,299,053.

[0150] As a nasal formulation, flurazepam may be administered in 25 to 250 μL metered sprays. In some preferred embodiments, flurazepam is administered in 50 to 150 μL, especially about 100 μL, metered sprays.

Lorazepam

[0151] The dosage of Lorazepam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.1 to about 10, preferably about 0.2 to about 1 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Lorazepam may be manufactured using the process disclosed in United States patent 3,296,249.

[0152] As a nasal formulation, lorazepam may be administered in 25 to 250 μL metered sprays. In some preferred embodiments, lorazepam is administered in 50 to 150 μL, especially about 100 μL, metered sprays.

Medazepam

[0153] The dosage of medazepam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.1 to about 10, preferably about 0.2 to about 1 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Medazepam may be manufactured using the process disclosed in United States patent 3,243,427.

[0154] As a nasal formulation, medazepam may be administered in 25 to 250 μL metered sprays. In some preferred embodiments, medazepam is administered in 50 to 150 μL, especially about 100 μL, metered sprays.

Mexazolam

[0155] The dosage of mexazolam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.1 to about 10, preferably about 0.2 to about 1 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Mexazolam may be manufactured using the process disclosed in United States patent 3,722,371.

[0156] As a nasal formulation, mexazolam may be administered in 25 to 250 μL metered sprays. In some preferred embodiments, mexazolam is administered in 50 to 150 μL, especially about 100 μL, metered sprays.

Midazolam

[0157] The dosage of midazolam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.1 to about 20, preferably about 0.2 to about 10 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Midazolam may be manufactured using the process disclosed in one of United States patents 4,280,957 or 5,831,089.

[0158] As a nasal formulation, midazolam may be administered in 25 to 250 µL metered sprays. In some preferred embodiments, midazolam is administered in 50 to 150 µL, especially about 100 µL, metered sprays.

Temazepam

[0159] The dosage of temazepam varies by indication, however it is expected that a therapeutic dose will be in the range of about 1 to about 50, preferably about 5 to about 30 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Temazepam may be manufactured using the process disclosed in United States patent 3,340,253 or 3,374,225.

[0160] As a nasal formulation, temazepam may be administered in 25 to 250 µL metered sprays. In some preferred embodiments, temazepam is administered in 50 to 150 µL, especially about 100 µL, metered sprays.

Formulation

[0161] Some embodiments comprise administering to one or more mucosal membranes of a patient a therapeutically effective amount of one or more benzodiazepine drugs, or pharmaceutically-acceptable salts thereof. Some embodiments of the composition disclose a composition comprising one or more benzodiazepine drugs or pharmaceutically-acceptable salts thereof in a concentration up to about 600 mg/mL. Other compositions disclose a composition comprising one or more benzodiazepine drugs or pharmaceutically-acceptable salts thereof in a concentration of about 10 mg/mL up to about 250 mg/mL. Further, some embodiments disclose a composition comprising one or more benzodiazepine drugs or pharmaceutically-acceptable salts thereof in a concentration of about 20 mg/mL up to about 50 mg/mL.

[0162] Some embodiments disclose a carrier system that is about 50% to about 90% (w/w) Vitamin E and about 10% to about 50% (w/w) lower alcohol or lower alkyl glycol, or any combinations thereof. Some embodiments disclose a carrier system that is about 65% to about 75% (w/w) Vitamin E and about 25% to about 35% (w/w) lower alkyl alcohol or lower alkyl glycol, or any combinations thereof. Further, some embodiments disclose a carrier system that is about 70% (w/w) Vitamin E and about 30% (w/w) lower alkyl alcohol or lower alkyl glycol, or any combinations thereof.

[0163] Some embodiments of the invention provide a method of administering the benzodiazepine drug composition to a patient. The preferred embodiment comprises use of diazepam. Some embodiments of the method disclose a dosage level of diazepam of about 1.0 mg to about 20.0 mg until achievement of the desired result. Other dosage levels disclose a dosage level of about 2.0 mg to about 15.0 mg until the desired result is achieved. Some embodiments disclose a dosage level of about 5.0 mg to about 10.0 mg until the desired result is achieved.

[0164] In some embodiments of the method, the dosage volume ranges from about 10 µL to about 200 µL. In some embodiments, the dosage volume ranges from about 20 µL to about 180 µL. Further, some embodiments disclose a dosage volume of about 50 µL to about 140 µL. In some embodiments, the dosage volume is 50 µL, 75 µL or 100 µL per nostril.

Formulation Process

[0165] In some embodiments, the composition for nasal administration is substantially free of benzodiazepine microparticles, nanoparticles or combinations thereof. In some embodiments, the composition is made by slowly warming or heating the Vitamin E until it is liquefied. Next, the one or more benzodiazepine drugs are added. The mixture is stirred and heated until the one or more benzodiazepine drugs dissolve or are substantially dissolved. Next, the one or more alcohols or glycols, or any combinations thereof, are added to the composition. This composition is stirred until a less viscous composition is achieved.

[0166] The formulation process may be adjusted to take into consideration variations in the formulation. For example, as depicted in Figure 4, formulations comprising both benzyl alcohol and ethanol may be formulated by first combining Vitamin E, benzyl alcohol and ethanol (*e.g.*, dehydrated alcohol, USP), mixing until the ingredients are homogenous, heating the mixture to about 45°C (±2°C), adding alkyl glocoside and mixing until the alkyl glycoside is dissolved and the solution is homogenous, adding benzodiazepine (*e.g,* diazepam) while maintaining the mixture at about 45 °C, cooling the solution to about 25°C (±2°C) and adding ethanol (Q.S.) to achieve the final target weight of solution, mixing well to assure homogeneity. Solutions manufactured according to this process may be formulated in different concentrations of diazepam. For example, some embodiments of the invention include diazepam formulations summarized in the following table. While diazepam is used as an illustration in Figure 4 and the following table, any benzodiazepines may also be used, such as alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, any pharmaceutically-acceptable salts thereof, and any combinations thereof.

[0167] NRL-1 Quantitative Composition. The formulations are for nasal administration.

Component	**Solution Concentration**		
	50mg/mL	**75 mg/mL**	**100 mg/mL**
Vitamin E	56.47 mg	56.47 mg	56.47 mg
Benzyl alcohol	10.50 mg	10.50 mg	10.50 mg
Diazepam	5.00 mg	7.50 mg	10.00 mg
Intravail A3®	0.25 mg	0.25 mg	0.25 mg
Dehydrated ethanol	q.s. to 100µL	q.s. to 100µL	q.s. to 100µL

[0168] In some embodiments, the aforementioned formulations are sterile solutions with a bacteria count of 10 below the allowable level on a per mL basis. Additionally, pathogens are preferably absent. In some embodiments, the solutions are self-preserving, self-sterile or both.

[0169] In some embodiments, the benzodiazepine drug is formulated as a microparticulate and/or nanoparticulate suspension of the benzodiazepine. Preparation of microparticulate and nanoparticulate benzodiazepine may be accomplished by methods such as milling, etc. Such methods are known to those skilled in the art.

[0170] Figure 5 depicts one embodiment of a process of manufacturing a suspension of benzodiazepine according to the instant invention. First, the benzodiazepine (*e.g.,* diazepam) is sieved to produce a micronized benzodiazepine (*e.g.,* diazepam). The micronized benzodiazepine (*e.g.*, diazepam) is then split into two intermediates products - Diazepam A (high pressure) is a small particle size (mean particle size < 2000 nm) and Diazepam B (low pressure) is a large particle size (mean particle diameter > 2000 nm). After in-process testing, the two intermediate products are combined with one or more excipients in correct proportions to produce a bimodal particle suspension having a pre-selected mean particle diameter, which in some embodiments is greater than 2000 nm. In some embodiments, the excipients are prepared according to the second column in Figure 5, *e.g.* by first combining propylene glycol, water and vitamin E polyethylene glycol succinate to form a mixture and heating the mixture until the ingredients are dissolved, then adding methylparaben, propyl paraben and Intravail™ (alkyl glycoside) to the mixture and mixing until the newly added ingredients are dissolved, and finally cooling the mixture, *e.g.* to 25°C ± 2°C. The excipients can then be combined with Micronized Diazepam A and Micronized Diazepam B and mixed vigorously to disperse the micronized Diazepam to form the suspension. Next, povidone is added to the mixture, which is mixed until the povidone is fully dissolved. Finally, the suspension is brought to its final target weight with purified water and mixed well to achieve homogeneity. The final product can then be filled into suitable containers. In some embodiments, 3 mL may be filled into 4 mL amber glass vials with PTFE lined phenolic closures, though other containers are of course possible and contemplated within the scope of the invention. As diazepam is depicted in Figure 5 as an exemplary benzodiazepine, any benzodiazepines, such as alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, any pharmaceutically-acceptable salts thereof, and any combinations thereof may also be employed.

[0171]

[0172] In some embodiments, the benzodiazepine drug is formulated as a solution. It is considered an aspect of the invention that employment of microparticulate and/or nanoparticulate benzodiazepine drug during the process of preparing the formulation, can improve the overall solubility of the benzodiazepine drug in the solvent system.

Additional Active and Inactive Ingredients

[0173] Additionally, some embodiments of the compositions and methods of using the compositions comprise an additional ingredient in the composition selected from active ingredients. By way of non-limiting example, such active ingredients include insulin, calcitonins (for example porcine, human, salmon, chicken, or eel) and synthetic modifications thereof, enkephalins, LHRH and analogues (Nafarelin, Buserelin, Zolidex), GHRH (growth hormone releasing hormone), nifedipin, THF (thymic humoral factor), CGRP (calcitonin gene related peptide), atrial natriuretic peptide, antibiotics, metoclopramide, ergotamine, Pizotizin, nasal vaccines (particularly HIV vaccines, measles, rhinovirus Type 13 and respiratory syncitial virus), pentamidine, CCK (Cholecystikinine), DDVAP, Interferons, growth hormone (solatotropir polypeptides or their derivatives (preferably with a molecular weight from 1000 to 300000), secretin, bradykinin antagonists, GRF (Growth releasing factor), THF, TRH (Thyrotropin releasing hormone), ACTH analogues, IGF (Insulin like growth factors), CGRP (Calcitorin gene related peptide) Atrial Natriuretic peptide, Vasopressin and analogues (DDAVP, Lypressin), Metoclopramide, Migraine treatment (Dihydroergotamine, Ergometrine, Ergotamine, Pizotizin), Nasal Vaccines (Particularly AIDS vaccines) FACTOR VIII, Colony Stimulating factors, G-CSF (granulocyte-colony stimulating factor), EPO (Erythropoitin) PTH (Parathyroid hormone) or pharmaceutically acceptable salts or combinations thereof.

[0174] Additionally, some embodiments of the compositions and methods of using the compositions comprise an additional ingredient in the composition selected from other anticonvulsants. By way of non-limiting example, such active ingredients include: paraldehyde; aromatic allylic alcohols (such as stiripentol); barbiturates (e.g. phenobarbitol, primidone, methylphenobarbital, metharbital and barbexaclone); bromides (such as potassium bromide); carbamates (such as felbamate); carboxamides (such as carbamazepine and oxcarbazepine); fatty acids (such as valproic acid, sodium valproate, and divalproex sodium, vigabatrin, progabide, tiagabine); fructose, topiramate, Gaba analogs (e.g. gabapentin and pregabalin); hydantoins (e.g. ethotoin, phenytoin, mephenytoin and fosphenytoin); oxazolidinediones (such as paramethadione, trimethadione, ethadione); propionates (e.g. beclamide), pyrimidinediones (e.g. primidone); pyrrolidines (e.g. brivaracetam, levetiracetam and seletracetam); succinimides (e.g. ethosuximide, phensuximide and mesuximide); sulfonamides (e.g. acetazolamide, sulthiame, methazolamide and zonisamide); triazines (such as lamotrigine); ureas (such as pheneturide, phenacemide); valproylamides (such as valpromide and valnoctamide); as well as other anticonvulsants or pharmaceutically acceptable salts or combinations thereof.

[0175] Additionally, some embodiments of the compositions and methods of using the compositions comprise an additional ingredient in the composition selected from other anticonvulsants. By way of non-limiting example, such active ingredients include: antibiotics and antimicrobial agents such as tetracyline hydrochloride, leucomycin, penicillin, penicillin derivatives, erythromycin, gentamicin, sulphathiazole and nitrofurazone; local anaesthetics such as benzocaine; vasoconstrictors such as phenylephrine hydrochloride, tetrahydrozoline hydrochloride, naphazoline nitrate, oxymetazoline hydrochloride and tramazoline hydrochloride; cardiotonics such as digitalis and digoxin; vasodilators such as nitroglycerine and papaverine hydrochloride; antiseptics such as chlorhexidine hydrochloride, hexylresorcinol, dequaliniumchloride and

ethacridine; enzymes such as lysozyme chloride, dextranase; bone metabolism controlling agents such as vitamin D, active vitamin D and vitamin C; sex hormones; hypotensives; sedatives; anti-tumor agents; steroidal anti-inflammatory agents such as hydrocortisone, prednisone, fluticasone, prednisolone, triamcinolone, triamcinolone acetonide, dexamethasone, betamethasone, beclomethasone, and beclomethasone dipropionate; non-steroidal anti-inflammatory agents such as acetaminophen, aspirin, aminopyrine, phenylbutazone, medanamic acid, ibuprofen, diclofenac sodium, indomethacine, colchicine, and probenocid; enzymatic anti-inflammatory agents such as chymotrypsin and bromelain seratiopeptidase; anti-histaminic agents such as diphenhydramine hydrochloride, chloropheniramine maleate and clemastine; anti-allergic agents and antitussive-expectorant antasthmatic agents such as sodium chromoglycate, codeine phosphate, and isoproterenol hydrochloride or pharmaceutically acceptable salts or combinations thereof.

[0176] Additionally, some embodiments of the compositions and methods of using the compositions comprise an additional inactive ingredient in the composition. By way of non-limiting example, minor amounts of ingredients such as stabilizers, coloring agents, pH adjusters, buffering agents, preservatives such as agents which may prevent degradation, wetting agents, and flavoring agents may also be present. Examples of coloring agents include β-carotene, Red No. 2 and Blue No. 1. Examples of preservatives include stearic acid, ascorbyl stearate and ascorbic acid. Examples of corrigents include menthol and citrus perfume.

[0177] In some embodiments, the drug delivery system of the invention may advantageously comprise an absorption enhancer. The term "enhancer", means any material which acts to increase absorption across the mucosa and/or increases bioavailability. In some embodiments, such materials include mucolytic agents, degradative enzyme inhibitors and compounds which increase permeability of the mucosal cell membranes. Whether a given compound is an "enhancer" can be determined by comparing two formulations comprising a non-associated, small polar molecule as the drug, with or without the enhancer, in an in vivo or good model test and determining whether the uptake of the drug is enhanced to a clinically significant degree. The enhancer should not produce any problems in terms of chronic toxicity because in vivo the enhancer should be non-irritant and/or rapidly metabolized to a normal cell constituent that does not have any significant irritant effect.

[0178] In some embodiments, preferred enhancing materials lysophospholipids, for example lysophosphatidylcholine obtainable from egg or soy lecithin. Other lysophosphatidylcholines that have different acyl groups as well as lyso compounds produced from phosphatidylethanolamines and phosphatidic acid which have similar membrane modifying properties may be used. Acyl carnitines (e.g. palmitoyl-dl-carnitine-chloride) is an alternative. In some embodiments, a suitable concentration is from 0.02 to 20% (w/v).

[0179] In some embodiments, enhancing agents that are appropriate include chelating agents (EGTA, EDTA, alginates), surface active agents (especially non-ionic materials), acyl glycerols, fatty acids and salts, tyloxapol and biological detergents listed in the SIGMA Catalog, 1988, page 316-321. Also agents that modify the membrane fluidity and permeability are appropriate such as enamines (e.g. phenylalanine enamine of ethylacetoacetate), malonates (e.g. diethyleneoxymethylene malonate), salicylates, bile salts and analogues and fusidates. Suitable concentrations are up to 20% (w/v).

[0180] In some embodiments, the invention takes advantage of delivery of a drug incorporated into or onto a bioadhesive microsphere with an added pharmaceutical adjuvant applies to systems that contain active drug and mucolytic agent, peptidase inhibitors or non-drug polypeptide substrate singly or in combination. Suitably mucolytic agents are thiol-containing compounds such as N-acetylcysteine and derivatives thereof. Peptide inhibitors include actinonin, amastatin, bestatin, chloroacetyl-HOLeu-Ala-Gly-NH.sub.2, diprotin A and B, ebelactone A and B, E-64, leupeptin, pepstatin A, phisphoramidon, H-Thr-(tBu)-Phe-Pro-OH, aprotinin, kallikrein, chymostatin, benzamidine, chymotrypsin and trypsin. Suitable concentrations are from 0.01 to 10% (w/v). The person skilled in the art will readily be able to determine whether an enhancer should be included.

Administration

[0181] In some embodiments, the administration of the composition comprises administering at least a portion of the therapeutically effective amount of the composition onto at least one mucosal membrane. In some embodiments, the administration of the composition comprises spraying at least a portion of the therapeutically effective amount of the composition into at least one nostril. In some embodiments, the administration of the composition comprises spraying at least a portion of the therapeutically effective amount of the composition into each nostril. In some embodiments, the administration of the composition comprises spraying a first quantity of the composition into the first nostril, spraying a second quantity of the composition into a second nostril, and optionally after a pre-selected time delay, spraying a third quantity of the composition into the first nostril. Some embodiments further comprise, optionally after a pre-selected time delay, administering at least a fourth quantity of the composition to the second nostril.

Alprazolam

[0182] The dosage of alprazolam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.5 to about 4, preferably about 1 to about 2 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Alprazolam may be manufactured using the process disclosed in United States patent 3,987,052.

[0183] As a nasal formulation, alprazolam may be administered in 25 to 250 μL metered sprays. In some preferred embodiments, alprazolam is administered in 50 to 150 μL, especially about 100 μL, metered sprays. In some embodiments, a first metered spray is applied to a first nostril and if necessary a second metered spray is applied to a second nostril. In some optional embodiments, a third metered spray is applied to the first nostril. In some embodiments, a fourth metered spray is applied to the second nostril. In some embodiments, additional metered sprays are applied to alternating nostrils until the full target therapeutic dose has been administered to the patient. In some embodiments, there is a time increment of from several seconds to 5 minutes, preferably about 10 seconds to about 1 minute, between applications of benzodiazepine drug to the same nostril. This allows time for the drug to cross the nasal mucosa and enter the blood stream. Multiple applications of metered sprays to each nostril, optionally separated by a time interval, allows administration of a full therapeutic dose in increments small enough to permit full absorption of the benzodiazepine drug into the blood stream and avoid loss of drug down the back of the throat.

Diazepam

[0184] The dosage of diazepam may vary by indication, however it is expected that a therapeutic dose will be in the range of about 1 to about 20, preferably about 2 to about 10 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Diazepam may be manufactured using the process disclosed in one of United States patents 3,371,085, 3,109,843, 3,136,815 or 3,102,116.

[0185] As a nasal formulation, diazepam may be administered in 25 to 250 μL metered sprays. In some preferred embodiments, diazepam is administered in 50 to 150 μL, especially about 100 μL, metered sprays. In some embodiments, a first metered spray is applied to a first nostril and if necessary a second metered spray is applied to a second nostril. In some optional embodiments, a third metered spray is applied to the first nostril. In some embodiments, a fourth metered spray is applied to the second nostril. In some embodiments, additional metered sprays are applied to alternating nostrils until the full target therapeutic dose has been administered to the patient. In some embodiments, there is a time increment of from several seconds to 5 minutes, preferably about 10 seconds to about 1 minute, between applications of benzodiazepine drug to the same nostril. This allows time for the drug to cross the nasal mucosa and enter the blood stream. Multiple applications of metered sprays to each nostril, optionally separated by a time interval, allows administration of a full therapeutic dose in increments small enough to permit full absorption of the benzodiazepine drug into the blood stream and avoid loss of drug down the back of the throat.

Flurazepam

[0186] The dosage of flurazepam varies by indication, however it is expected that a therapeutic dose will be in the range of about 5 to 40, preferably about 20 to about 35 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Flurazepam may be manufactured using the process disclosed in United States patent 3,567,710 or 3,299,053.

[0187] As a nasal formulation, flurazepam may be administered in 25 to 250 μL metered sprays. In some preferred embodiments, flurazepam is administered in 50 to 150 μL, especially about 100 μL, metered sprays. In some embodiments, a first metered spray is applied to a first nostril and if necessary a second metered spray is applied to a second nostril. In some optional embodiments, a third metered spray is applied to the first nostril. In some embodiments, a fourth metered spray is applied to the second nostril. In some embodiments, additional metered sprays are applied to alternating nostrils until the full target therapeutic dose has been administered to the patient. In some embodiments, there is a time increment of from several seconds to 5 minutes, preferably about 10 seconds to about 1 minute, between applications of benzodiazepine drug to the same nostril. This allows time for the drug to cross the nasal mucosa and enter the blood stream. Multiple applications of metered sprays to each nostril, optionally separated by a time interval, allows administration of a full therapeutic dose in increments small enough to permit full absorption of the benzodiazepine drug into the blood stream and avoid loss of drug down the back of the throat.

Lorazepam

[0188] The dosage of Lorazepam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.1 to about 10, preferably about 0.2 to about 1 mg per dose, from 1 to 8, preferably from

2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Lorazepam may be manufactured using the process disclosed in United States patent 3,296,249.

[0189] As a nasal formulation, lorazepam may be administered in 25 to 250 μL metered sprays. In some preferred embodiments, lorazepam is administered in 50 to 150 μL, especially about 100 μL, metered sprays. In some embodiments, a first metered spray is applied to a first nostril and if necessary a second metered spray is applied to a second nostril. In some optional embodiments, a third metered spray is applied to the first nostril. In some embodiments, a fourth metered spray is applied to the second nostril. In some embodiments, additional metered sprays are applied to alternating nostrils until the full target therapeutic dose has been administered to the patient. In some embodiments, there is a time increment of from several seconds to 5 minutes, preferably about 10 seconds to about 1 minute, between applications of benzodiazepine drug to the same nostril. This allows time for the drug to cross the nasal mucosa and enter the blood stream. Multiple applications of metered sprays to each nostril, optionally separated by a time interval, allows administration of a full therapeutic dose in increments small enough to permit full absorption of the benzodiazepine drug into the blood stream and avoid loss of drug down the back of the throat.

Medazepam

[0190] The dosage of medazepam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.1 to about 10, preferably about 0.2 to about 1 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Medazepam may be manufactured using the process disclosed in United States patent 3,243,427.

[0191] As a nasal formulation, medazepam may be administered in 25 to 250 μL metered sprays. In some preferred embodiments, medazepam is administered in 50 to 150 μL, especially about 100 μL, metered sprays. In some embodiments, a first metered spray is applied to a first nostril and if necessary a second metered spray is applied to a second nostril. In some optional embodiments, a third metered spray is applied to the first nostril. In some embodiments, a fourth metered spray is applied to the second nostril. In some embodiments, additional metered sprays are applied to alternating nostrils until the full target therapeutic dose has been administered to the patient. In some embodiments, there is a time increment of from several seconds to 5 minutes, preferably about 10 seconds to about 1 minute, between applications of benzodiazepine drug to the same nostril. This allows time for the drug to cross the nasal mucosa and enter the blood stream. Multiple applications of metered sprays to each nostril, optionally separated by a time interval, allows administration of a full therapeutic dose in increments small enough to permit full absorption of the benzodiazepine drug into the blood stream and avoid loss of drug down the back of the throat.

Mexazolam

[0192] The dosage of mexazolam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.1 to about 10, preferably about 0.2 to about 1 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Mexazolam may be manufactured using the process disclosed in United States patent 3,722,371.

[0193] As a nasal formulation, mexazolam may be administered in 25 to 250 µL metered sprays. In some preferred embodiments, mexazolam is administered in 50 to 150 µL, especially about 100 µL, metered sprays. In some embodiments, a first metered spray is applied to a first nostril and if necessary a second metered spray is applied to a second nostril. In some optional embodiments, a third metered spray is applied to the first nostril. In some embodiments, a fourth metered spray is applied to the second nostril. In some embodiments, additional metered sprays are applied to alternating nostrils until the full target therapeutic dose has been administered to the patient. In some embodiments, there is a time increment of from several seconds to 5 minutes, preferably about 10 seconds to about 1 minute, between applications of benzodiazepine drug to the same nostril. This allows time for the drug to cross the nasal mucosa and enter the blood stream. Multiple applications of metered sprays to each nostril, optionally separated by a time interval, allows administration of a full therapeutic dose in increments small enough to permit full absorption of the benzodiazepine drug into the blood stream and avoid loss of drug down the back of the throat.

Midazolam

[0194] The dosage of midazolam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.1 to about 20, preferably about 0.2 to about 10 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Midazolam may be manufactured using the process disclosed in one of United States patents 4,280,957 or 5,831,089.

[0195] As a nasal formulation, midazolam may be administered in 25 to 250 µL metered sprays. In some preferred embodiments, midazolam is administered in 50 to 150 µL, especially about 100 µL, metered sprays. In some embodiments, a first metered spray is applied to a first nostril and if necessary a second metered spray is applied to a second nostril. In some optional embodiments, a third metered spray is applied to the first nostril. In some embodiments, a fourth metered spray is applied to the second nostril. In some embodiments, additional metered sprays are applied to alternating nostrils until the full target therapeutic dose has been administered to the patient. In some embodiments, there is a time increment of from several seconds to 5 minutes, preferably about 10 seconds to about 1 minute, between applications of benzodiazepine drug to the same nostril. This allows time for the drug to cross the nasal mucosa and enter the blood stream. Multiple applications of metered sprays to each nostril, optionally separated by a time interval, allows administration of a full therapeutic dose in increments small enough to permit full absorption of the benzodiazepine drug into the blood stream and avoid loss of drug down the back of the throat.

Temazepam

[0196] The dosage of temazepam varies by indication, however it is expected that a therapeutic dose will be in the range of about 1 to about 50, preferably about 5 to about 30 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Temazepam may be manufactured using the process disclosed in United States patent 3,340,253 or 3,374,225.

[0197] As a nasal formulation, temazepam may be administered in 25 to 250 µL metered sprays. In some preferred embodiments, temazepam is administered in 50 to 150 µL, especially about 100 µL, metered sprays. In some embodiments, a first metered spray is applied to a first nostril and if necessary a second metered

spray is applied to a second nostril. In some optional embodiments, a third metered spray is applied to the first nostril. In some embodiments, a fourth metered spray is applied to the second nostril. In some embodiments, additional metered sprays are applied to alternating nostrils until the full target therapeutic dose has been administered to the patient. In some embodiments, there is a time increment of from several seconds to 5 minutes, preferably about 10 seconds to about 1 minute, between applications of benzodiazepine drug to the same nostril. This allows time for the drug to cross the nasal mucosa and enter the blood stream. Multiple applications of metered sprays to each nostril, optionally separated by a time interval, allows administration of a full therapeutic dose in increments small enough to permit full absorption of the benzodiazepine drug into the blood stream and avoid loss of drug down the back of the throat.

[0198] Those skilled in the art will be aware that a systematic, therapeutically effective amount of benzodiazepine drugs for treating the aforementioned disorders will vary with age, size, weight, and general physical condition of the patient as well as the severity of the disease. Frequency of administration will likewise vary with the formulation of the composition and it can be adjusted so that any suitable number of doses per day may be used.

Examples

[0199] The invention will now be illustrated with reference to the following illustrative, non-limiting examples.

Example 1

[0200] A pharmaceutical composition comprising diazepam is prepared. It is formulated as a solution to be delivered via a nasal delivery device. The composition is used to treat or prevent seizures associated with epilepsy in adults. Treatment is administered either before or after a seizure has begun. If the patient is seizing, it is administered as 1 puff from any nasal delivery device (1 puff at 5.0 mg/puff (5.0 mg/0.1 mL and 0.1 mL/puff)) every 5 minutes until cessation of the seizure. However, it can be given as 1 puff per nostril in each nostril (2 puffs at 2.5 mg/puff (5.0 mg/0.1 mL and 0.05 mL/puff)) every 5 minutes until cessation of the seizure. The composition according to this example is set forth in the following table.

Table 1-1 (not claimed)

5.0 mg/0.1mL	Diazepam
70.0 mg	α-tocopherol
0.1 mL	ethanol (qs ad to 0.1 mL)

Example 2

[0201] A pharmaceutical composition comprising diazepam is prepared. It is formulated as a solution to be delivered via a nasal delivery device. The composition is used to treat or prevent seizures associated with epilepsy in children. Treatment is administered either before or after a seizure has begun. If the patient is seizing, it is administered as 1 puff from any nasal delivery device (1 puff at 2.0 mg/puff (2.0 mg/0.1 mL and 0.1 mL/puff)). If the seizure fails to stop another dose may be administered after 5 minutes. However, it can be given as 1 puff per nostril in each nostril (2 puffs at 1.0 mg/puff (2.0 mg/0.1 mL and 0.05 mL/puff)). If the seizure fails to stop another dose may be administered after 5 minutes. The composition according to this example is set forth in the following table.

Table 2-1 (not claimed)

2.0 mg/0.1mL	Diazepam
70.0 mg	α-tocopherol
0.1 mL	ethanol (qs ad to 0.1 mL)

Example 3 – Formulation of Diazepam Solutions

[0202] In general, benzodiazepine solutions may be formulated by combining one or more natural or synthetic tocopherols or tocotrienols and one or more lower alcohols or glycols and mixing until a homogeneous mixture is formed, adding the benzodiazepine drug to the homogeneous mixture, heating and mixing the ingredients until the benzodiazepine is fully dissolved in the homogeneous mixture, cooling the mixture, and bringing the mixture to its final mass or volume with lower alcohol or glycol.

[0203] Two different diazepam solutions were formulated by the foregoing process. Vitamin E USP and dehydrated ethanol USP were combined in the amounts set forth in the following table and mixed to form a homogeneous mixture. Diazepam in the amounts set forth in the following table was then added to the homogeneous mixture. The ingredients were heated to 40-45°C with mixing until the diazepam was fully dissolved, thereby forming a solution. The solution was cooled to 20-25°C, whereupon the solution was brought to its final target weight with dehydrated ethanol USP and the solution was mixed thoroughly to assure homogeneity. The solution was then sampled for in-process testing and packaged in 3 mL amber glass vials.

Table 3-1: Diazepam Solutions – 70 mg/mL (not claimed)

Component	Solution 00 (65% Vitamin E) Concentration (mg/mL)	Solution 02 (80% Vitamin E) Concentration (mg/mL)
Diazepam USP	70.0	70.0
Vitamin E USP	650.0	800.0
Dehydrated Ethanol USP	q.s. to 1 mL	q.s. to 1 mL

[0204] Additional solutions of diazepam at varying concentrations are made in a similar manner, by varying the amount of diazepam and the relative amounts of Vitamin E and ethanol. Other benzodiazepine solutions are made by substituting one or more benzodiazepines for diazepam. Other ingredients, such as alkyl glycoside, can be added at a suitable step in the process (e.g. before or concurrently with the addition of benzodiazepine).

Example 5 -- Stability of Diazepam Solutions

[0205] Solutions 00 and 02 (Example 3) were set up on stability at 25°C / 60% RH, 30°C / 65% RH and 40°C / 75% RH. One batch each of the two different formulations, packaged in 3-ml vials with screw-top closures, along with corresponding actuators, were set up at three storage conditions. They are listed in Table 1 with their corresponding Particle Sciences initial sample control numbers.

Table 5-1: Summary of PSI sample control numbers

Formulation #	25°C/60% RH	30°C/65% RH	40°C/75% RH
Solution 00 – 70 mg/ml solution, 65% Vitamin E	083101.01	083101.02	083101.02
Solution 02 – 70 mg/ml solution, 80% vitamin E	083102.01	083102.02	083102.03

[0206] Summaries of the average assay values and all other results are given in Tables 5-4, 5-5,. The results for the initial, 1-month and 3-month time points are also shown for comparison. Individual spray content uniformity results are given in Tables 5-8, 5-9, 5-10, and 5-11..

[0207] In general, all of the assays and the other results are similar to the initial data, with the exceptions of diazepam related compounds A and B.

[0208] Related compound A did not meet the specification of not more than (NMT) 0.01% for some samples (see Table 2). Related compound A has increased with time and temperature.

Table 5-2: Summary of related compound A T6M results

Solution/Suspension #	25°C/60% RH	30°C/65% RH	40°C/75% RH
Solution 00	Meets specification	0.058%	0.051%
Solution 02	Meets specification	Meets specification	Meets specification

[0209] Related compound B is also increasing with time and temperature, and now fails specification of NMT 0.1% at 40°C condition for both suspension and one solution formulation. Only formulation 2602 meets all impurity specifications.

Table 5-3: Summary of related compound B T6M results

Solution/Suspension #	25°C/60% RH	30°C/65% RH	40°C/75% RH
Solution 00	Meets specification	Meets specification	0.398%

Solution 02	Meets specification	Meets specification	Meets specification

Table 5-4: Summary of Solution 00 results

Solution 00, 70mg/ml, 65% Vitamin E	**Specifications**	**Initial**	**1 month 25°C/ 60 %RH**	**1 month 30°C/ 65 %RH**	**1 month 40°C/ 75 %RH**	**3 month 25°C/ 60 %RH**	**3 month 30°C/ 65 %RH**	**3 month 40°C/ 75 %RH**	**6 month 25°C/ 60 %RH**	**6 month 30°C/ 65 %RH**	**6 month 40°C/ 75 %RH**
Description	Yellow to orange solution	Amber solution	Amber solution	Amber solution	Amber solution	Amber solution	Amber solution	Amber solution	Amber solution	Amber solution	Amber solution
Identification – UV	Conforms to reference std. UV and RT	pass	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Assay Diazepam (%)	90.0 to 110.0%	100.1	100.3	93.9	98.8	96.3	96.9	101.2	97.5	94.6	100.6
Impurities (%) [1]											
Nordazepam	NMT 0.3%	0.005	0.01	0.014	0.019	0.013	0.013	0.013	0.013	0.013	0.013
Related Compound B	NMT 0.1%	ND	0.002	0.007	0.03	0.008	0.016	0.089	0.024	0.098	0.398
Related Compound A	NMT 0.01%	0.002	0.002	0.004	0.011	0.002	0.002	0.01	0.005	0.058	0.051
Unknown	NMT 0.1%	0.011	0.012	0.014	0.02	0.037	0.039	0.047	0.035	0.066	0.055
Total	NMT 1.0%	0.0	0.0	0.0	0.1	0.1	0.1	0.2	0.1	0.2	0.5
Microbial Limits	Meets USP {61}	pass	N/A	N/A	N/A	N/A	N/A	N/A	pass	not tested	not tested
Fill weight (g)	report results	1.108	1.105	1.111	1.112	1.109	1.109	1.113	1.103	1.111	1.109
Fill volume (ml)	report results	1.192	1.189	1.195	1.196	1.193	1.193	1.198	1.187	1.195	1.193
Spray delivered (µl)	report results	133.9	140.7	146.8	140.5	149.1	143.5	139.6	131.4	not tested	136.4
Average Spray Content (%)	report results	95.0	101.2	100.4	99.4	99.7	94.6	99.4	95.7	not tested	108.7
Viscosity (Pa*s)	report results	0.14	0.086	0.12	0.12	0.096	0.14	0.12	0.12	0.11	0.11

[1] LOQ is approximately 0.006%, LOD is approximately 0.002%. Results below LOQ are reported in this table for trending purposes.

Table 5-5: Summary of Solution 02 results

Solution 02, 70mg/ml, 65% Vitamin E	**Specifica -tions**	**Initial**	**1 month 25°C/ 60 %RH**	**1 month 30°C/ 65 %RH**	**1 month 40°C/ 75 %RH**	**3 month 25°C/ 60 %RH**	**3 month 30°C/ 65 %RH**	**3 month 40°C/ 75 %RH**	**6 month 25°C/ 60 %RH**	**6 month 30°C/ 65 %RH**	**6 month 40°C/ 75 %RH**
Description	Yellow to orange sol'n	Amber sol'n	Amber sol'n	Amber sol'n	Amber sol'n	Amber sol'n	Amber sol'n	Amber sol'n	Amber sol'n	Amber sol'n	Amber sol'n
Identification – UV	Con-forms to reference std. UV and RT	pass	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Assay Diazepam (%)	90.0 to 110.0%	100.5	94.9	96.2	103.3	98.0	97.2	99.6	97.0	94.3	100.3
Impurities (%) (1)											
Nordazepam	NMT 0.3%	0.003	0.004	0.005	0.006	0.005	0.005	0.006	0.005	0.004	0.005
Related Compound B	NMT 0.1%	ND	0.002	0.003	0.006	0.003	0.005	0.032	0.007	0.020	0.058
Related Compound A	NMT 0.01%	0.003	0.002	0.002	0.003	0.002	0.002	0.004	0.003	0.009	0.007
Unknown	NMT 0.1%	0.01	0.012	0.014	0.018	0.019	0.025	0.032	0.014	0.020	0.018
Total	NMT 1.0%	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.1	0.1
Microbial Limits	Meets USP {61}	pass	N/A	N/A	N/A	N/A	N/A	N/A	pass	not tested	not tested
Fill weight (g)	report results	1.135	1.117	1.128	1.123	1.116	1.133	1.137	1.124	1.133	1.127
Fill volume (ml)	report results	1.184	1.165	1.177	1.172	1.164	1.182	1.186	1.172	1.183	1.176
Spray delivered (µl)	report results	115.0	137.5	137.6	133.1	143.9	136.3	143.8	129.3	not tested	124.2
Average Spray Content (%)	report results	98.6	97.6	97.7	100.7	98.7	94.7	100.5	95.8	not tested	97.1
Viscosity (Pa*s)	report results	0.69	0.68	0.64	0.68	0.63	0.65	0.64	0.61	0.55	0.56

(1) LOQ is approximately 0.006%, LOD is approximately 0.002%. Results below LOQ are reported in this table for trending purposes.

Table 5-8: Solution 00 25°C/60% RH spray content uniformity results

Sample	Weight Collected, g	Weight Actuated, g	Diazepam Recovered, mg	% Diazepam Recovered
1	0.13061	0.13259	9.59355	97.89
2	0.13217	0.13451	9.78206	99.82
3	0.12365	0.13332	8.85797	90.39
4	0.12761	0.13072	9.39720	95.89
5	0.14702	0.15216	8.91438	90.96
6	0.13414	0.13702	9.22442	94.13
7	0.12959	0.13384	9.84590	100.47
8	0.12367	0.14603	8.88093	90.62
9	0.13367	0.13425	9.92610	101.29
Average	0.13135	0.13716	9.380	95.72
St. Dev.	0.0070	0.0071	0.4309	4.3970
% RSD	5.35	5.20	4.59	4.59

Table 5-9: Solution 00 40°C/75% RH spray content uniformity results

Sample	**Weight Collected, g**	**Weight Actuated, g**	**Diazepam Recovered, mg**	**% Diazepam Recovered**
1	0.14139	0.15111	10.57237	107.88
2	0.14731	0.15146	11.62831	118.66
3	0.14489	0.14684	10.94206	111.65
4	0.14237	0.14873	11.94883	121.93
5	0.12188	0.13415	9.78103	99.81
6	0.12756	0.13047	9.78347	99.83
7	0.13549	0.13841	10.45221	106.66
8	0.12323	0.12543	9.41177	96.04
9	0.14299	0.14517	11.35701	115.89
Average	0.13635	0.14131	10.653	108.70
St. Dev.	0.0097	0.0095	0.8884	9.0649
% RSD	7.14	6.76	8.34	8.34

Table 5-10: Solution 02 25°C/60% RH spray content uniformity results

Sample	Weight Collected, g	Weight Actuated, g	Diazepam Recovered, mg	% Diazepam Recovered
1	0.12280	0.12611	8.88043	90.62
2	0.13318	0.13549	9.55581	97.51
3	0.13260	0.13452	9.71837	99.17
4	0.12064	0.12305	9.48123	96.75
5	0.13215	0.13582	9.34463	95.35
6	0.13559	0.13790	9.48722	96.81
7	0.13158	0.13371	9.43613	96.29
8	0.13357	0.13495	9.79164	99.91
9	0.12165	0.12443	8.84732	90.28
Average	0.12931	0.13178	9.394	95.85
St. Dev.	0.0058	0.0056	0.3303	3.3701
% RSD	4.52	4.25	3.52	3.52

Table 5-11: Solution 02 40°C/75% RH spray content uniformity results

Sample	Weight Collected, g	Weight Actuated, g	Diazepam Recovered, mg	% Diazepam Recovered
1	0.12336	0.12563	9.02005	92.04
2	0.05723	0.05792	9.43076	96.23
3	0.13554	0.13908	9.93829	101.41
4	0.13619	0.13679	9.87755	100.79
5	0.13227	0.13414	9.64403	98.41
6	0.13331	0.13515	9.80808	100.08
7	0.13455	0.13844	9.31952	95.10
8	0.13314	0.13736	9.28106	94.70
9	0.13249	0.13387	9.32935	95.20
Average	0.12423	0.12649	9.517	97.11
St. Dev.	0.0254	0.0260	0.3148	3.2119
% RSD	20.45	20.57	3.31	3.31

Example 6

[0210] All of the solutions described in Example 3 and formulated as described in Example 3, with the addition of a suitable amount of an alkyl glycoside, as described herein, such as dodecyl maltoside, tetradecyl maltoside, sucrose dodecanoate, sucrose monostearate, sucrose distearate, and/or combinations of two or more thereof, or marketed as Intravail® by Aegis Therapeutics, San Diego, CA. The solutions with added alkyl glycoside may then be put up on stability as described in Example 5, *mutatis mutandis*.

Example 7

[0211] The solutions of Examples 3 and 6 are evaluated for pharmacokinetics in a suitable animal model, such as in mice, rats, rabbits or dogs. First each animal (e.g. rabbit) is administered an amount of a benzodiazepine drug intravenously. The amount of intravenously dosed benzodiazepine drug is selected to be less, e.g. roughly half, of what is considered an effective dose administered nasally. For example, the intravenous dose of diazepam administered to rabbits is about 0.05 to about 0.2 mg/kg, e.g. about 0.1 mg/kg. Blood is collected immediately before administration and at specific time points post-administration. Plasma blood levels of the drug are assayed for each of the blood samples. After at least a one day washout period, each animal is administered, intranasally, an amount of a solution as described in Examples 3 and 6. Blood is collected immediately before administration and at substantially the same specific time points as the IV dose post-administration. Pharmacokinetic curves (blood plasma concentration of drug versus time) are constructed for the intravenous route of administration and for each of the solutions administered by the intranasal administration route.

[0212] Toxicity is assessed by known means. In particular, histological samples are collected from the nasal mucosal tissues of the test animals. Other toxological methods are optionally employed as well.

Example 8

[0213] The solutions of Examples 3 and 6 are evaluated for their ability to deliver drug across the blood brain barrier in a suitable animal model, such as in mice, rats, rabbits or dogs. Each animal is administered, intranasally, an amount of a solution as described in Examples 3 and 6, with the solution optionally containing an imaging agent, such as a dye, that may be used as a proxy for determining the ability of the drug to cross the blood brain barrier. The drug or imaging agent is detected at selected time points after administration of the or solution to determine how well the drug or imaging agent crosses the blood brain barrier. These results may be compared with analogous result obtained with an intravenous solution containing the drug or imaging agent.

Example 9

[0214] The above-described solutions can be evaluated for pharmacokinetics in humans. Normal, healthy human test subjects are administered an amount of the drug intravenously. The amount chosen for intravenous administration may be any amount, but is conveniently a dose that is considered effective in treating seizure in humans. For example, an IV dose of diazepam administered to humans may be in the range of 1 to 15 mg, e.g. about 7.5 mg. Blood is collected immediately before administration and at selected time points after administration. Plasma blood levels of the drug are assayed for each of the blood samples. After at least a one day washout period, each subject is administered, intranasally, an amount of a solution as described herein. Blood is collected immediately before administration and at substantially the same time points after administration as the intravenous time points. Pharmacokinetic curves (blood plasma concentration of drug versus time) are constructed for the intravenous and intranasal administration routes.

Example 10

[0215] The above-described solutions can be evaluated for efficacy in a suitable animal model. Briefly, for each dose of solution to be tested, a test animal is stimulated with a seizure inducing stimulus. The stimulus may be light, sound, chemical or other stimulus effective to induce seizure in the model animal. Once the animal has begun to seize, a solution as described herein is administered intranasally to the animal. The efficacy of the dose of the solution is evaluated based upon the animal's response to the test dose. This procedure is repeated through sufficient iterations, and at sufficient numbers of doses, to identify a dose that is considered effective to treat seizure by intranasal administration of the drug.

Example 11

[0216] A pharmaceutical composition comprising diazepam was prepared as a composition formulated as a solution to be delivered via a nasal delivery device. The solution was prepared according to the procedure outlined in the flow diagram of Figure 4. The ingredients used in the 100 mg/mL diazepam solution are set forth in Table 11-1, below:

Table 11-1

Ingredient	Concentration (% (w/v))
Diazepam	10.00 % (w/v)
α-tocopherol*	56.47 % (w/v)
Ethanol (dehydrated)	q.s. ((~18.07) % (w/v))
Intravail A3**	0.25 % (w/v)
Benzyl alcohol	10.50 % (w/v)

*Vitamin E, **Dodecyl maltoside

[0217] A batch of solution of Table 11-1 was prepared and subjected to stability testing at 25°C/60% R.H. for 12 months. The following table provides stability determinations for this batch at initial, 3 month, 6 month and 12 month time points.

[0218]

Test Parameter	Initial % Label Claim (100 mg/mL)	1 Month	3 Month	6 Month
Appearance	Pale amber to amber solution	Amber solution	Amber solution	Amber solution
Diazepam % Label Claim	103.3	99.5	99.2	99.1

[0219] A batch of solution of Table 11-1 was prepared and subjected to stability testing at 30°C/65% R.H. (accelerated conditions) for 12 months. The following table provides stability determinations for this batch at initial, 1 month and 12 month time points.

Test Parameter	Initial % Label Claim (100 mg/mL)	1 Month	6 Month
Appearance	Pale amber to amber solution	Amber solution	Amber solution
Diazepam % Label Claim	103.3	97.8	99.7

[0220] A batch of solution of Table 11-1 was prepared and subjected to stability testing at 40°C/75% R.H. (accelerated conditions) for 12 months. The following table provides stability determinations for this batch at initial, 3 month, 6 month and 12 month time points.

Test Parameter	Initial % Label Claim (100 mg/mL)	1 Month	3 Month	6 Month
Appearance	Pale amber to amber solution	Amber solution	Amber solution	Amber solution
Diazepam % Label Claim	103.3	97.9	100.0	99.4

[0221] The suspension formulation is set forth in Table 11-2 (not claimed), below

Component	Function	Concentration (mg/mL)
Diazepam	Active	100.0
Methyl Paraben	Preservative	2.0
Propyl Paraben	Preservative	0.5
Intravail A3	Absorption aid	2.5
Vitamin E TPGS	Dispersant	10.0
Propylene Glycol	Dispersant	100.0
Povidone	Suspending agent	5.0
Water	Carrier	q.s. to 1.0 mL

[0222] A batch of suspension of Table 11-2 was prepared and subjected to stability testing at 25°C/60% R.H. for 3 months. The following table provides stability determinations for this batch at initial and 3 month time points.

Test Parameter	Initial % Label Claim (100 mg/mL)	3 Month
Appearance	Opaque white liquid	Opaque white liquid
Diazepam % Label Claim	104.4	102.1

[0223] A batch of suspension of Table 11-2 was prepared and subjected to stability testing at 30°C/65% R.H. (accelerated conditions) for 1 month. The following table provides stability determinations for this batch at initial and 1 month time points.

Test Parameter	Initial % Label Claim (100 mg/mL)	1 Month
Appearance	Opaque white liquid	Opaque white liquid
Diazepam % Label Claim	104.4	102.9

[0224] A batch of suspension of Table 11-2 was prepared and subjected to stability testing at 40°C/75% R.H. (accelerated conditions) for 3 months. The following table provides stability determinations for this batch at initial, 1 month and 3 month time points.

Test Parameter	Initial % Label Claim (100 mg/mL)	1 Month	3 Month
Appearance	Opaque white liquid	Opaque white liquid	White liquid
Diazepam % Label Claim	104.4	102.7	108.7

[0225] A three-period, three-treatment, six-sequence, randomized cross-over study was conducted in healthy volunteers. For each dose, each volunteer was domiciled for at least 12 hours prior to each dose and until after a 24 hour pharmacokinetic sample was collected. Single doses of 100 µL of the pharmaceutical compositions described in Tables 11-1 and 11-2 were administered to each volunteer as one spray to the left nostril of 100 µL per spray. Pharmacokinetic samples were collected at 22 time points over 10 days. (PK time points: 2.5, 5, 10, 15, 20, 30 and 45 minutes, 1, 1.5, 2, 4, 12, 24, 36, 48, 72, 96, 144, 192 and 240 hours after each dose.) No

serious adverse events were noted. PK data were compared with those obtained with 5 mg of diazepam administered intravenously. The PK data are summarized in Table 11-3 and Figures 1-3.

[0226] The solution of Table 11-1 and the suspension of Table 11-2 were found to be well-tolerated with only mild adverse events reported. The solution of Table 11-1 was further found to have similar bioavailability to intravenous administration of diazepam (96% of i.v.) The intranasal formulation of Table 11-1 exhibited a Tmax of 1.5 hours, a Cmax of approximately 272 ng/mL. These results are comparable to those reported in the literature for commercially available diazepam gel (Diastat®).

[0227] Solutions similar to those set forth in Table 11-1 can be prepared consisting of: diazepam (5-15 % (w/v)), dodecyl maltoside (0.01-1 % (w/v)), vitamin E (45-65 % (w/v)), ethanol (10-25 % (w/v)) and benzyl alcohol (5-15 % (w/v)); diazepam (9-11 % (w/v)), dodecyl maltoside (0.1-0.5 % (w/v)), vitamin E (50-60 % (w/v)), ethanol (15-22.5 % (w/v)) and benzyl alcohol (7.5-12.5 % (w/v)); or diazepam (10 % (w/v)), dodecyl maltoside (0.15-0.3 % (w/v)), vitamin E (50-60 % (w/v)), ethanol (17-20 % (w/v)) and benzyl alcohol (10-12 % (w/v)).

[0228] Solutions similar to those set forth in Table 11-1 achieve bioavailability that is from about 80-125% of that achieved with the same benzodiazepine administered intravenously, *e.g.* bioavailability that is from about 90-110% of that achieved with the same benzodiazepine administered intravenously or about 92.5 to 107.5% that obtained with the same benzodiazepine administered intravenously. Such solutions may be used in methods of treating a patient with a disorder which may be treatable with a benzodiazepine drug, such as seizure, epileptic seizure and/or breakthrough seizure. In some embodiments, solutions described herein may be used to treat a disorder such as is treated with Diastat® diazepam gel.

[0229] A summary of pharmacokinetic data obtained for the solution and a suspension form of diazepam is shown below in Table 11-3:

Table 11-3

Summary of Pharmacokinetic Parameters for Intranasal (10 mg) and IV (5 mg) Diazepam

	Diazepam Nasal Spray (10 mg/100µL)				Diazepam Injection	
	NRL-1.A Suspension		NRL-1.B Solution		5 mg/mL IV	
Parameter [a]	n	Mean (SD) [b]	n	Mean (SD) [b]	n	Mean (SD) [b]
C_{max} (ng/mL)	24	221 (78.6)	24	272 (100)	24	555 (316)
T_{max} (h) [b]	24	1.00 (0.6, 2.0)	24	1.50 (0.8, 4.0)	24	0.03 (0.03, 0.50)
AUC_{0-t} (h×ng/mL)	24	5229 (1463)	24	7340 (1882)	24	3832 (1150)
$AUC_{0-\infty}$ (h×ng/mL)	20	5381 (1409)	20	7338 (2072)	24	4104 (1318)
λz (h^{-1})	20	0.0142 (0.0053)	20	0.0155 (0.0046)	24	0.0142 (0.0055)
$t_{½}$ (h)	20	56.2 (23.0)	20	49.2 (16.9)	24	56.2 (21.0)

a: Mean values are presented as arithmetic means.
b: Median (min, max) reported for T_{max}

[0230] The data collected in the study are further illustrated in Figures 1-3. Figure 1 is a linear scale plot of the arithmetic mean of the plasma concentration of diazepam after intranasal (IN) administration of 10 mg of

diazepam as the suspension of Table 11-2 and after IN administration of 10 mg of diazepam as a solution of Table 11-1 compared to intravenous (IV) administration of 5 mg of diazepam. Figure 2 is a semi-logarithmic scale plot of the same data shown in Figure 1. Figure 3 shows the first 24 hours of data from Figure 1 on a linear scale.

Main Request
Claims

1. A pharmaceutical solution for use in a method of treating seizures by nasal administration of said pharmaceutical solution which consists of:

(a) a benzodiazepine drug;

(b) one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from 30% to 95% (w/w);

(c) 1-25% (w/v) ethanol and 1-25% (w/v) benzyl alcohol, in a combined amount from 10% to 50% (w/w);

(d) an alkyl glycoside; and

(e) optionally at least one additional active pharmaceutical ingredient or excipient.

2. The pharmaceutical solution for use according to claim 1, wherein the benzodiazepine drug is selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, any pharmaceutically-acceptable salts thereof, and any combinations thereof.

Former Claim 3: deleted:

3. The pharmaceutical solution for use according to claim 2, containing 1 to 20% (w/v) of benzodiazepine.

4. The pharmaceutical solution for use according to claim 3, containing 1 to 20% (w/v) of diazepam.

5. The pharmaceutical solution for use according to claim 1, wherein the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β- tocotrienol, γ-tocotrienol, δ- tocotrienol, tocophersolan, any isomers thereof, any esters thereof, any analogs thereof, and any combinations thereof.

6. The pharmaceutical solution for use according to claim 1, containing 10-22.5% (w/v) ethanol and 7.5-12.5% (w/v) benzyl alcohol.

7. The pharmaceutical solution for use according to claim 1, wherein the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from 45% to 85% (w/w).

8. The pharmaceutical solution for use according to claim 1, consisting of 5-15% (w/v) diazepam, 0.01-1% (w/v) alkyl glycoside, 45-65% (w/v) vitamin E, 10-25% (w/v) ethanol and 5-15% (w/v) benzyl alcohol.

9. The pharmaceutical solution for use according to claim 1, wherein the pharmaceutically-acceptable formulation comprises at least 0.01% (w/w) of an alkyl glycoside.

10. The pharmaceutical solution for use according to claim 9, wherein the pharmaceutically-acceptable formulation comprises 0.01% to 1% (w/w) of dodecyl maltoside.

11. The pharmaceutical solution for use according to claim 1, consisting of diazepam, vitamin E, ethanol, benzyl alcohol, and dodecyl maltoside.

12. The pharmaceutical solution for use according to claim 1, consisting of 5-15% (w/v) diazepam, 45-65% (w/v) vitamin E, 10-25% (w/v) ethanol, 5-15% (w/v) benzyl alcohol, and 0.01%-1% (w/v) dodecyl maltoside.

13. The pharmaceutical solution for use according to claim 1, consisting of 10% (w/v) diazepam, 56.47% (w/v) vitamin E, q.s. dehydrated ethanol, 10.5% (w/v) benzyl alcohol, and 0.25% (w/v) dodecyl maltoside.

Auxiliary Request 2
Claims

1. A pharmaceutical solution for use in a method of treating seizures by nasal administration of said pharmaceutical solution which consists of:

(a) a benzodiazepine drug;

(b) one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from 30% to 95% (w/w);

(c) 10-22.5% (w/v) ethanol and 7.5 to 12.5% (w/v) benzyl alcohol, in a combined amount from 10% to 50% (w/w); and

(d) an alkyl glycoside.

2. The pharmaceutical solution for use according to claim 1, wherein the benzodiazepine drug is selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, any pharmaceutically-acceptable salts thereof, and any combinations thereof.

3. The pharmaceutical solution for use according to claim 2, containing 1 to 20% (w/v) of benzodiazepine.

4. The pharmaceutical solution for use according to claim 3, containing 1 to 20% (w/v) of diazepam.

5. The pharmaceutical solution for use according to claim 1, wherein the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β- tocotrienol, γ-tocotrienol, δ- tocotrienol, tocophersolan, any isomers thereof, any esters thereof, any analogs thereof, and any combinations thereof.

6. The pharmaceutical solution for use according to claim 1, wherein the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from 45% to 85% (w/w).

7. The pharmaceutical solution for use according to claim 1, wherein the pharmaceutically-acceptable formulation comprises at least 0.01% (w/w) of an alkyl glycoside.

8. The pharmaceutical solution for use according to claim 7, wherein the pharmaceutically-acceptable formulation comprises 0.01% to 1% (w/w) of dodecyl maltoside.

9. The pharmaceutical solution for use according to claim 1, consisting of diazepam, vitamin E, ethanol, benzyl alcohol, and dodecyl maltoside.

Auxiliary Request 1
Claims

1. A pharmaceutical solution for use in a method of treating seizures by nasal administration of said pharmaceutical solution which consists of:

(a) a benzodiazepine drug;

(b) one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from 30% to 95% (w/w);

(c) 1-25% (w/v) ethanol and 1-25% (w/v) benzyl alcohol, in a combined amount from 10% to 50% (w/w); and

(d) an alkyl glycoside

.

2. The pharmaceutical solution for use according to claim 1, wherein the benzodiazepine drug is selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, any pharmaceutically-acceptable salts thereof, and any combinations thereof.

3. The pharmaceutical solution for use according to claim 2, containing 1 to 20% (w/v) of benzodiazepine.

4. The pharmaceutical solution for use according to claim 3, containing 1 to 20% (w/v) of diazepam.

5. The pharmaceutical solution for use according to claim 1, wherein the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β- tocotrienol, γ-tocotrienol, δ- tocotrienol, tocophersolan, any isomers thereof, any esters thereof, any analogs thereof, and any combinations thereof.

6. The pharmaceutical solution for use according to claim 1, containing 10-22.5% (w/v) ethanol and 7.5-12.5% (w/v) benzyl alcohol.

7. The pharmaceutical solution for use according to claim 1, wherein the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from 45% to 85% (w/w).

8. The pharmaceutical solution for use according to claim 1, consisting of 5-15% (w/v) diazepam, 0.01-1% (w/v) alkyl glycoside, 45-65% (w/v) vitamin E, 10-25% (w/v) ethanol and 5-15% (w/v) benzyl alcohol.

9. The pharmaceutical solution for use according to claim 1, wherein the pharmaceutically-acceptable formulation comprises at least 0.01% (w/w) of an alkyl glycoside.

10. The pharmaceutical solution for use according to claim 9, wherein the pharmaceutically-acceptable formulation comprises 0.01% to 1% (w/w) of dodecyl maltoside.

11. The pharmaceutical solution for use according to claim 1, consisting of diazepam, vitamin E, ethanol, benzyl alcohol, and dodecyl maltoside.

12. The pharmaceutical solution for use according to claim 1, consisting of 5-15% (w/v) diazepam, 45-65% (w/v) vitamin E, 10-25% (w/v) ethanol, 5-15% (w/v) benzyl alcohol, and 0.01%-1% (w/v) dodecyl maltoside.

13. The pharmaceutical solution for use according to claim 1, consisting of 10% (w/v) diazepam, 56.47% (w/v) vitamin E, q.s. dehydrated ethanol, 10.5% (w/v) benzyl alcohol, and 0.25% (w/v) dodecyl maltoside.

ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

~~CROSS-REFERENCE TO RELATED APPLICATIONS~~

~~[001] This application claims priority to United States provisional application 61/497,017, filed June 14, 2011 and United States provisional application 61/570,110, filed December 13, 2011, each of which is incorporated herein by reference in its entirety.~~

FIELD OF THE INVENTION

~~[002]~~[001] This application relates to the nasal administration of benzodiazepine drugs and combinations thereof.

BACKGROUND OF THE INVENTION

~~[003]~~[002] By way of non-limiting example, the benzodiazepine family consists of drugs such as diazepam, lorazepam, and midazolam. The drugs in this family have been observed as possessing sedative, tranquilizing and muscle relaxing properties. They are frequently classified as anxiolytic and skeletal muscle relaxants. They are thought to be useful in preventing, treating, or ameliorating the symptoms of anxiety, insomnia, agitation, seizures (such as those caused by epilepsy), muscle spasms and rigidity, the symptoms of drug withdrawal associated with the continuous abuse of central nervous system depressants, and exposure to nerve agents.

~~[004]~~[003] Benzodiazepines are thought to act by binding to the $GABA_A$ receptor of a neuron, possibly causing the receptor to change shape and making it more accessible to gama-aminobutyric acid (GABA).

~~[005]~~[004] GABA is an inhibitory neurotransmitter that, when bound to the $GABA_A$ receptor, facilitates Cl^- ions flooding into the neuron to which the receptor is bound. The increase in Cl^- ions hyperpolarizes the membrane of the neuron. This completely or substantially reduces the ability of the neuron to carry an action potential. Targeting this receptor is particularly useful in treating many disorders, such as tetanus and epilepsy, which may result from too many action potentials proceeding through the nervous system.

~~[006]~~[005] Current formulations of benzodiazepine drugs can be administered orally, rectally, or parenterally. The ability to utilize these and other types of formulations has been significantly limited due, in many cases, to solubility challenges.

~~[007]~~[006] The oral route of administration may be considered sub-optimal due to several disadvantages. For example, the amount of time required for an orally administered benzodiazepine drug to reach therapeutically relevant concentrations in blood plasma may be rather long, such as an hour or more. Moreover, as benzodiazepine drugs pass through the liver a significant amount of the drug may be metabolized. Thus, large doses may be required to achieve therapeutic plasma levels. Furthermore, due to the nature of seizures and muscle spasms, it can be extremely difficult for either a patient or a care-giver to administer the benzodiazepine drug orally and care-givers may be reluctant to place their hands in patients' mouths.

~~[008]~~[007] Intravenous administration perhaps provides a faster route of administration. However intravenous administration is generally limited to trained health care professionals in tightly controlled clinical settings. Additionally, sterility must be maintained. Furthermore, administering any drug intravenously can be painful and is likely impractical for patients suffering from a phobia of needles. In addition, intravenous administration of benzodiazepines is associated with respiratory depression. Thus, use of intravenous benzodiazepines is limited to professional health care environments.

~~[009]~~[008] Rectal suppository compositions of benzodiazepine drugs can have a rapid onset of action. However, the inconvenience of rectally administered drug 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 care-givers.

SUMMARY OF THE INVENTION

[009] The invention refers to a pharmaceutical solution for use in a method of treating seizures by nasal administration of said pharmaceutical solution which consists of: (a) a benzodiazepine drug; (b) one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from 30% to 95% (w/w); (c) 1-25% (w/v) ethanol and 1-25% (w/v) benzyl alcohol, in a combined amount from 10% to 50% (w/w); and (d) an alkyl glycoside.

[010] In some embodiments, there are provided (non-aqueous) pharmaceutical solutions as defined in the claims for use as defined in the claims ~~nasal administration consisting of: (a) a benzodiazepine drug; (b) one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); (c) one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w); and (d) an alkyl glycoside, in a pharmaceutically acceptable solution~~ for administration to one or more nasal mucosal membranes of a patient. ~~In some embodiments, t~~The benzodiazepine drug is dissolved in the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); and the one or more alcohols ~~or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w)~~as defined in the claims. In some embodiments, the benzodiazepine drug is selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, any pharmaceutically-acceptable salts thereof, and any combinations thereof. In some embodiments, the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof. In some embodiments, the solution contains about 1 to about 20 % (w/v) of benzodiazepine, e.g. about 1 to about 20 % (w/v) of diazepam. In some embodiments, the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β- tocotrienol, γ- tocotrienol, δ- tocotrienol, tocophersolan, any isomers thereof, any esters thereof, any analogs or derivatives thereof, and any combinations thereof. ~~In some embodiments, the one or more alcohols are selected from the group consisting of: ethanol, propyl alcohol,~~

~~butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, or any combinations thereof~~. ~~In some embodiments, t~~The solution contains ~~two or more alcohols, such as~~ ethanol (1-25 % (w/v)) and benzyl alcohol (1-25 % (w/v)), or ethanol (10-22.5 % (w/v)) and benzyl alcohol (7.5-12.5 % (w/v)), wherein the combined amounts are 10% to 50%. In some embodiments, the benzodiazepine is present in the pharmaceutical composition in a concentration from about 20 mg/mL to about 200 mg/mL. In some embodiments, the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from about 45% to about 85% (w/w). In some embodiments, the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from about 50% to about 75% (w/w). In some embodiments, the ~~one or more~~ alcohols ~~or glycols, or any combinations thereof, is~~are in an amount from about 15% to ~~about 55~~50% (w/w), e.g. about 25% to about 40% (w/w). In some embodiments, the solution consists of diazepam (5-15 % (w/v)), alkyl glycoside (0.01-1 % (w/v)), vitamin E (45-65 % (w/v)), ethanol (10-25 % (w/v)) and benzyl alcohol (5-15 % (w/v)). In some embodiments, the solution comprises at least about 0.01% (w/w) of an alkyl glycoside, *e.g.* about 0.01% to 1% (w/w) of an alkyl glycoside, such as dodecyl maltoside. In some embodiments, the solution consists of diazepam (5-15 % (w/v)), dodecyl maltoside (0.01-1 % (w/v)), vitamin E (45-65 % (w/v)), ethanol (10-25 % (w/v)) and benzyl alcohol (5-15 % (w/v)); more particularly the solution may consist of diazepam (9-11 % (w/v)), dodecyl maltoside (0.1-0.5 % (w/v)), vitamin E (50-60 % (w/v)), ethanol (15-22.5 % (w/v)) and benzyl alcohol (7.5-12.5 % (w/v)); and even more particularly, the solution may consist of diazepam (10 % (w/v)), dodecyl maltoside (0.15-0.3 % (w/v)), vitamin E (50-60 % (w/v)), ethanol (17-20 % (w/v)) and benzyl alcohol (10-12 % (w/v)).

[011] ~~Some embodiments described herein provide~~The pharmaceutical solution is for use in a method of treating a patient with a disorder which may be treatable with a benzodiazepine drug, comprising: administering to one or more nasal mucosal membranes of a patient ~~a~~ said pharmaceutical solution for nasal administration ~~consisting of a benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w); and an alkyl glycoside~~. In some embodiments, the benzodiazepine drug is dissolved in the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); and the ~~one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w)~~alcohols as defined in the claims. ~~In some embodiments, the benzodiazepine drug is selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, any pharmaceutically acceptable salts thereof, and any combinations thereof. In some embodiments, the benzodiazepine drug is diazepam, or a pharmaceutically acceptable salt thereof. In some embodiments, the solution contains about 1 to about 20 % (w/v) of benzodiazepine, e.g. about 1 to about 20 % (w/v) of diazepam. In some embodiments, the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α tocopherol, β tocopherol, γ tocopherol, δ tocopherol, α tocotrienol, β-~~

~~tocotrienol, γ- tocotrienol, δ- tocotrienol, tocophersolan, any isomers thereof, any esters thereof, any analogs or derivatives thereof, and any combinations thereof. In some embodiments, the one or more alcohols are selected from the group consisting of: ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, or any combinations thereof. In some embodiments, the solution contains two or more alcohols, such as ethanol (1-25 % (w/v)) and benzyl alcohol (1-25 % (w/v)), or ethanol (10-22.5 % (w/v)) and benzyl alcohol (7.5-12.5 % (w/v)).~~ In some embodiments, the benzodiazepine is present in the pharmaceutical composition in a concentration from about 20 mg/mL to about 200 mg/mL. In some embodiments, the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from about 45% to about 85% (w/w). In some embodiments, the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from about 50% to about 75% (w/w). ~~In some embodiments, the one or more alcohols or glycols, or any combinations thereof, is in an amount from about 15% to about 55% (w/w), e.g. about 25% to about 40% (w/w).~~ In some embodiments, the solution consists of diazepam (5-15 % (w/v)), alkyl glycoside (0.01-1 % (w/v)), vitamin E (45-65 % (w/v)), ethanol (10-25 % (w/v)) and benzyl alcohol (5-15 % (w/v)). In some embodiments, the solution comprises at least about 0.01% (w/w) of an alkyl glycoside, *e.g.* about 0.01% to 1% (w/w) of an alkyl glycoside, such as dodecyl maltoside. In some embodiments, the solution consists of diazepam (5-15 % (w/v)), dodecyl maltoside (0.01-1 % (w/v)), vitamin E (45-65 % (w/v)), ethanol (10-25 % (w/v)) and benzyl alcohol (5-15 % (w/v)); more particularly the solution may consist of diazepam (9-11 % (w/v)), dodecyl maltoside (0.1-0.5 % (w/v)), vitamin E (50-60 % (w/v)), ethanol (15-22.5 % (w/v)) and benzyl alcohol (7.5-12.5 % (w/v)); and even more particularly, the solution may consist of diazepam (10 % (w/v)), dodecyl maltoside (0.15-0.3 % (w/v)), vitamin E (50-60 % (w/v)), ethanol (17-20 % (w/v)) and benzyl alcohol (10-12 % (w/v)). In some embodiments, the patient is human. In some embodiments, the benzodiazepine is administered in a therapeutically effective amount from about 1 mg to about 20 mg. In some embodiments, the benzodiazepine is administered as in a dosage volume from about 10 µL to about 200 µL. In some embodiments, the administration of the pharmaceutical composition comprises spraying at least a portion of the therapeutically effective amount of the benzodiazepine into at least one nostril. In some embodiments, the administration of the pharmaceutical composition comprises spraying at least a portion of the therapeutically effective amount of the benzodiazepine into each nostril. In some embodiments, administration of the pharmaceutical composition comprises spraying a first quantity of the pharmaceutical composition into the first nostril, spraying a second quantity of the pharmaceutical composition into a second nostril, and optionally after a pre-selected time delay, spraying a third quantity of the pharmaceutical composition into the first nostril. In some embodiments, the method further comprises, optionally after a pre-selected time delay, administering at least a fourth quantity of the pharmaceutical composition to the second nostril. In some embodiments, nasal administration of the pharmaceutical composition begins at any time before or after onset of symptoms of a disorder which may be treatable with the pharmaceutical composition. In some embodiments, the treatment achieves bioavailability that is from about 80-125% (e.g. about 90-110%, or more particularly about 92.5-107.5%) of that achieved with the same benzodiazepine administered intravenously, e.g. In this context, it is intended that

bioavailability be determined by a suitable pharmacodynamic method, such as comparison of area under the blood plasma concentration curve (AUC) for the nasally and intravenously administered drug. It is further understood that the percent bioavailability of the nasally administered benzodiazepine may be determined by comparing the area under the blood plasma concentration curve obtained with one dose of the benzodiazepine (e.g. 10 mg of nasal diazepam) with another dose of the same benzodiazepine administered intravenously (e.g. 5 mg of i.v. diazepam), taking into consideration the difference in dose. Thus, for the sake of illustration, a 10 mg nasal diazepam dose that achieves an AUC that is precisely half of the AUC obtained with 5 mg of i.v. diazepam would have a bioavailability of 100%. In some embodiments, the disorder to be treated is a seizure, such as an epileptic seizure, a breakthrough seizure, or other seizure. In some embodiments, the solution and treatment with the solution are substantially non-irritating and well-tolerated.

[012] ~~In some embodiments, the pharmaceutical composition for nasal administration comprises: a benzodiazepine drug; one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); and one or more alcohols or glycols, or any combinations thereof, in an amount from about 5% to about 70% (w/w), preferably about 10% to about 70% (w/w) in a pharmaceutically acceptable formulation for administration to one or more nasal mucosal membranes of the patient. In some embodiments the benzodiazepine drug is dissolved in the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); and the one or more alcohols or glycols, or any combinations thereof, in an amount from about 5% to about 70% (w/w), preferably about 10% to about 70% (w/w).~~ In some embodiments, the benzodiazepine drug is dissolved in a carrier system. In some embodiments, at least part of the benzodiazepine drug is in a form comprising benzodiazepine microparticles, nanoparticles or combinations thereof. In some embodiments, the composition is substantially free of benzodiazepine microparticles, nanoparticles or combinations thereof.

[013] In some embodiments, the benzodiazepine drug is selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, any pharmaceutically-acceptable salts thereof, and any combinations thereof. In some embodiments, the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof. In some embodiments, the benzodiazepine drug comprises benzodiazepine microparticles, nanoparticles, or combinations thereof. In some embodiments, the benzodiazepine nanoparticles have an effective average particle size of less than about 5000 nm. In some embodiments, the benzodiazepine drug is substantially free of benzodiazepine microparticles, nanoparticles or combinations thereof.

[014] In some embodiments, the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ- tocotrienol, δ- tocotrienol, tocophersolan, any isomers thereof, any esters thereof, any analogs or derivatives thereof, and any combinations thereof. In some embodiments, a synthetic tocopherol can

include Vitamin E TPGS (Vitamin E polyethylene glycol succinate). In some embodiments, on the other hand, synthetic tocopherols exclude tocopherols covalently bonded or linked (e.g. through a diacid linking group) to a glycol polymer, such as polyethylene glycol). Thus, in some embodiments, the compositions described herein exclude Vitamin E TPGS.

~~[015] In some embodiments, one or more alcohols are selected from the group consisting of: ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, or any combinations thereof. In some embodiments, the one or more glycols are selected from the group consisting of: ethylene glycol, propylene glycol, butylene glycol, pentylene glycol, any isomers thereof, and any combinations thereof. In some preferred embodiments, the glycols exclude glycol polymers. In some preferred embodiments, the glycols exclude glycol polymers having an average molecular weight of greater than 200. In some embodiments, the glycols exclude polyethylene glycol having an average molecular weight of greater than about 200.~~

~~[016]~~[015] In some embodiments, the benzodiazepine drug is present in the carrier system in a concentration from about 1 mg/mL to about 600 mg/mL. In some embodiments, the benzodiazepine drug is present in a carrier system in a concentration from about 10 mg/mL to about 250 mg/mL. In some embodiments, the benzodiazepine is present in a carrier system in a concentration from about 20 mg/mL to about 50 mg/mL.

~~[017]~~[016] In some embodiments, the carrier system comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 45% to about 85% (w/w). In some embodiments, the carrier system comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 60% to about 75% (w/w). In some embodiments, the carrier system comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount of about 70% (w/w).

~~[018]~~[017] ~~In some embodiments, the carrier system comprises one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w).~~ In some embodiments, the carrier system comprises ~~one or more~~said alcohols or glycols~~, or any combinations thereof,~~ in an amount from about 15% to ~~about 55~~50% (w/w). In some embodiments, the carrier system comprises ~~one or more~~said alcohols ~~or glycols, or any combinations thereof,~~ in an amount from about 25% to about 40% (w/w). In some embodiments, the carrier system comprises ~~one or more~~said alcohols ~~or glycols, or any combinations thereof,~~ in an amount of about 30% (w/w).

~~[019]~~[018] In some embodiments, the composition comprises at least one additional ingredient selected from the group consisting of: active pharmaceutical ingredients; ~~enhancers;~~ and excipients, such as enhancers; and agents used to adjust the pH, buffer the composition, prevent degradation, and improve appearance, odor, or taste.

~~[020]~~[019] In some embodiments, the composition comprises one or more additional excipients, such as one or more parabens, one or more povidones, and/or one or more alkyl glycosides.

~~[021]~~[020] The ~~invention also discloses~~pharmaceutical solution is for use in a method of treating a patient with a disorder that may be treatable with a benzodiazepine drug as defined in the claims. In some

embodiments, the patient is a human. ~~In some embodiments, the method comprises: administering to one or more nasal mucosal membranes of a patient a pharmaceutical composition for nasal administration comprising a benzodiazepine drug; one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); and one or more alcohols or glycols, or any combinations thereof, in an amount from about 5% to about 70%, preferably about 10% to about 70% (w/w). In some embodiments, the benzodiazepine is dissolved in the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); and the one or more alcohols or glycols, or any combinations thereof, in an amount from about 5% to about 70%, preferably about 10% to about 70% (w/w). In some embodiments, the benzodiazepine drug is dissolved in a carrier system.~~ In some embodiments, the benzodiazepine drug includes benzodiazepine microparticles, nanoparticles, or combinations thereof. In some embodiments, the composition is substantially free of benzodiazepine microparticles, nanoparticles or combinations thereof.

~~[022]~~[021] In some embodiments, the benzodiazepine drug is selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, or any pharmaceutically-acceptable salts thereof, and any combinations thereof. In some embodiments, the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof. In some embodiments, the benzodiazepine drug is fully dissolved in a single phase comprising one or more one or more natural or synthetic tocopherols or tocotrienols and one or more alcohols or glycols. In some embodiments, the benzodiazepine drug comprises benzodiazepine microparticles, nanoparticles, or combinations thereof. In some such embodiments, the composition further comprises water. In some embodiments, the benzodiazepine nanoparticles have an effective average particle size of less than about 5000 nm. In some embodiments, the composition is substantially free of benzodiazepine microparticles, nanoparticles or combinations thereof.

~~[023]~~[022] In some embodiments, the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ- tocotrienol, δ- tocotrienol, tocophersolan, any isomers thereof, any esters thereof, any analogs or derivatives thereof, and any combinations thereof.

~~[024]~~[023] In some embodiments, ~~the one or more alcohols are selected from the group consisting of: ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, and any combinations thereof. In some embodiments,~~ the pharmaceutical solution contains one or more glycols which can be~~are~~ selected from the group consisting of: ethylene glycol, propylene glycol, butylene glycol, pentylene glycol, any isomers thereof, and any combinations thereof. In some embodiments, the alcohol or glycol is free of water (dehydrated, USP). In some embodiments, the alcohol is ethanol (dehydrated, USP).

~~[025]~~[024] In some embodiments, the benzodiazepine drug is present in the carrier system in a concentration from about 1 mg/mL to about 600 mg/mL. In some embodiments, the benzodiazepine drug is present in the carrier system in a concentration of from about 10 mg/mL to about 250 mg/mL. In some

embodiments, the benzodiazepine drug is present in the carrier system in a concentration of from about 20 mg/mL to about 50 mg/mL.

~~[026]~~[025] In some embodiments, the carrier system comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 45% to about 85% (w/w). In some embodiments, the carrier system comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 60% to about 75% (w/w). In some embodiments, the carrier system comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount of about 70% (w/w).

~~[027] In some embodiments, the carrier system comprises one or more alcohols or glycols, or any combinations thereof, in an amount from about 15% to about 55% (w/w). In some embodiments, the carrier system comprises one or more alcohols or glycols, or any combinations thereof, in an amount from about 25% to about 40% (w/w). In some embodiments, the carrier system comprises one or more alcohols or glycols, or any combinations thereof, in an amount from about 30% (w/w).~~

~~[028]~~[026] In some embodiments, the composition comprises at least one additional ingredient selected from the group consisting of: active pharmaceutical ingredients; enhancers; excipients; and agents used to adjust the pH, buffer the composition, prevent degradation, and improve appearance, odor, or taste.

~~[029]~~[027] In some embodiments, the composition is in a pharmaceutically-acceptable spray formulation, and further comprising administering the composition to one or more nasal mucosal membranes of the patient. In some embodiments, the therapeutically effective amount is from about 1 mg to about 20 mg of the benzodiazepine. In some embodiments, the pharmaceutical composition is in a pharmaceutically-acceptable spray formulation having volume from about 10 µL to 200 µL.

~~[030]~~[028] In some embodiments, the administration of the composition comprises spraying at least a portion of the therapeutically effective amount of the composition into at least one nostril. In some embodiments, the administration of the composition comprises spraying at least a portion of the therapeutically effective amount of the composition into each nostril. In some embodiments, the administration of the composition comprises spraying a first quantity of the composition into the first nostril, spraying a second quantity of the composition into a second nostril, and optionally after a pre-selected time delay, spraying a third quantity of the composition into the first nostril. Some embodiments further comprise, optionally after a pre-selected time delay, administering at least a fourth quantity of the composition to the second nostril.

~~[031]~~[029] In some embodiments, the administration of the composition begins at any time before or after onset of symptoms of a disorder which may be treatable with the composition.

~~[032]~~[030] Additional ~~embodiments, uses, and~~ advantages of the invention will become apparent to the person skilled in the art upon consideration of the disclosure set forth herein.

~~INCORPORATION BY REFERENCE~~

~~[033] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.~~

BRIEF DESCRIPTION OF THE DRAWINGS

~~[034]~~[031] Some embodiments of the invention may be further appreciated upon consideration of the appended drawings, of which:

~~[035]~~[032] Figure 1 depicts a 240 hour linear plot of the arithmetic mean plasma concentration of diazepam after intranasal administration of 10 mg of diazepam as a suspension of Table 11-2, intranasal administration 10 mg of diazepam as a solution of Table 11-1, and 5 mg of diazepam as an intravenous injection.

~~[036]~~[033] Figure 2 depicts a 240 hour semi-logarithmic plot of the arithmetic mean plasma concentration of diazepam after intranasal administration of 10 mg of diazepam as a suspension of Table 11-2, intranasal administration 10 mg of diazepam as a solution of Table 11-1, and 5 mg of diazepam as an intravenous injection.

~~[037]~~[034] Figure 3 depicts a 24 hour linear plot of the arithmetic mean plasma concentration of diazepam after intranasal administration of 10 mg of diazepam as a suspension of Table 11-2, intranasal administration 10 mg of diazepam as a solution of Table 11-1, and 5 mg of diazepam as an intravenous injection.

~~[038]~~[035] Figure 4 is a Flow Diagram for one embodiment of a process for the manufacture of a diazepam solution according to the instant invention.

~~[039]~~[036] Figure 5 is a Flow Diagram for one embodiment of a process for the manufacture of a diazepam suspension according to the instant invention.

DETAILED DESCRIPTION OF THE INVENTION

~~[040]~~[037] Provided herein are pharmaceutical compositions of one or more benzodiazepine drugs ~~and~~ for use in methods ~~of using such pharmaceutical compositions~~as defined in the claims. Such pharmaceutical compositions are administered nasally.

~~[041] In some embodiments, the pharmaceutical composition for nasal administration comprises: a benzodiazepine drug; one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); and one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w) in a pharmaceutically acceptable formulation for administration to one or more nasal mucosal membranes of the patient. In some embodiments the benzodiazepine drug is dissolved in the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); and the one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w). In some~~

~~embodiments, the benzodiazepine drug is dissolved in a carrier system. In some embodiments, at least part of the benzodiazepine drug is in a form of microparticles, nanoparticles, or combinations thereof. In some embodiments, the composition is substantially free of benzodiazepine microparticles, nanoparticles or combinations thereof.~~

~~[042] In some embodiments, the pharmaceutical composition for nasal administration comprises: a benzodiazepine drug; one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); and one or more alcohols or glycols, or any combinations thereof, in an amount from about 5% to about 70% (w/w) in a pharmaceutically acceptable formulation for administration to one or more nasal mucosal membranes of the patient. In some embodiments the benzodiazepine drug is dissolved in the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); and the one or more alcohols or glycols, or any combinations thereof, in an amount from about 5% to about 70% (w/w). In some embodiments, the benzodiazepine drug is dissolved in a carrier system. In some embodiments, at least part of the benzodiazepine drug is in a form of microparticles, nanoparticles, or combinations thereof. In some embodiments, the composition is substantially free of benzodiazepine microparticles, nanoparticles or combinations thereof.~~

~~[043]~~[038] In some embodiments, the benzodiazepine drug is selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, any pharmaceutically-acceptable salts thereof, and any combinations thereof. In some embodiments, the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof. In some embodiments, the benzodiazepine drug comprises benzodiazepine microparticles, nanoparticles, or combinations thereof. In some embodiments, the benzodiazepine nanoparticles have an effective average particle size of less than about 5000 nm. In some embodiments, the composition is substantially free of benzodiazepine microparticles, nanoparticles or combinations thereof.

~~[044]~~[039] In some embodiments, the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ- tocotrienol, δ- tocotrienol, tocophersolan, any isomers thereof, any esters thereof, any analogs or derivatives thereof, and any combinations thereof. In some embodiments, the carrier system includes one or more synthetic tocopherols having a polymer glycol covalently bonded or linked to a tocopherol core, such as Vitamin E TPGS, which is described in United States Patent No. 6,193,985~~, which is incorporated herein by reference in its entirety~~. In particular, it has been found that in some particulate suspensions of benzodiazepines, wherein the benzodiazepine is not dissolved in a tocopherol phase, Vitamin E TPGS can be a desirable excipient for stabilizing the particulate (microparticle, nanoparticle or combination) suspension. In some embodiments, on the other hand, the carrier system specifically excludes synthetic tocopherols having a polymer glycol covalently bonded or linked to a tocopherol core, such as Vitamin E TPGS, which is described in United States Patent No. 6,193,985~~, which is incorporated herein by reference in its entirety~~.

(markup)

~~[045]~~[040] ~~In some embodiments, one or more alcohols are selected from the group consisting of: ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, or any combinations thereof. In some embodiments, the~~One alcohol is ethanol (dehydrated, USP). In some embodiments, the one or more additional glycols are selected from the group consisting of: ethylene glycol, propylene glycol, butylene glycol, pentylene glycol, any isomers thereof, and any combinations thereof. In some embodiments, the glycol is propylene glycol USP. In some embodiments, a synthetic tocopherol can include Vitamin E TPGS (Vitamin E polyethylene glycol succinate). In some embodiments, on the other hand, synthetic tocopherols exclude tocopherols covalently bonded or linked (e.g. through a diacid linking group) to a glycol polymer, such as polyethylene glycol). Thus, in some embodiments, the compositions described herein exclude Vitamin E TPGS.

~~[046]~~[041] In some embodiments, the benzodiazepine drug is present in the carrier system in a concentration from about 1 mg/mL to about 600 mg/mL. In some embodiments, the benzodiazepine drug is present in a carrier system in a concentration from about 10 mg/mL to about 250 mg/mL. In some embodiments, the benzodiazepine is present in a carrier system in a concentration from about 20 mg/mL to about 50 mg/mL.

~~[047]~~[042] In some embodiments, the carrier system comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 45% to about 85% (w/w). In some embodiments, the carrier system comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 60% to about 75% (w/w). In some embodiments, the carrier system comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount of about 70% (w/w). In some embodiments, a synthetic tocopherol can include Vitamin E TPGS (Vitamin E polyethylene glycol succinate). In some embodiments, on the other hand, synthetic tocopherols exclude tocopherols covalently bonded or linked (e.g. through a diacid linking group) to a glycol polymer, such as polyethylene glycol). Thus, in some embodiments, the compositions described herein exclude Vitamin E TPGS.

~~[048]~~[043] ~~In some embodiments, t~~The carrier system comprises ~~one or more~~said alcohols ~~or glycols, or any combinations thereof,~~ in an amount from ~~about~~ 10% to ~~about 55~~50%, ~~about~~ 10% to about 40%, ~~about~~ 10% to about 35%, about 12% to ~~about 55~~50%, about 12% to about 40%, about 12% to about 35%, about 15% to ~~about 55~~50%, about 15% to about 40%, about 15% to about 35%, ~~about~~ 10%, about 12.5%, about 15%, about 17.5%, about 20%, about 22.5%, about 25%, about 27.5%, about 30%, about 32.5%, about 35%, about 37.5%, about 40%, about 42.5%, about 45%, about 47.5%, ~~about~~ 50%~~, about 52.5% or about 55%~~ (w/w). In some embodiments, the carrier system comprises ~~one or more~~said alcohols ~~or glycols, or any combinations thereof,~~ in an amount from about 25% to about 40% (w/w). In some embodiments, the carrier system comprises one or more alcohols or glycols, or any combinations thereof, in an amount of about 30% (w/w). ~~In some embodiments, the alcohol is ethanol or contains ethanol.~~ In some preferred embodiments, the glycols exclude glycol polymers. In some preferred embodiments, the glycols exclude glycol polymers having

an average molecular weight of greater than 200. In some embodiments, the glycols exclude polyethylene glycol having an average molecular weight of greater than about 200.

~~[049]~~[044] In some embodiments, the carrier system comprises ~~one or more~~said alcohols ~~or glycols, or any combinations thereof,~~ in an amount from about 15% to ~~about 55~~50% (w/w). In some embodiments, the carrier system comprises ~~one or more~~said alcohols ~~or glycols, or any combinations thereof,~~ in an amount from about 25% to about 40% (w/w). In some embodiments, the carrier system comprises ~~one or more~~said alcohols ~~or glycols, or any combinations thereof,~~ in an amount of about 30% (w/w).

~~[050]~~[045] In some embodiments, the composition comprises at least one additional ingredient selected from the group consisting of: active pharmaceutical ingredients; enhancers; excipients; and agents used to adjust the pH, buffer the composition, prevent degradation, and improve appearance, odor, or taste.

~~[051]~~[046] In some embodiments, the compositions comprise at least one alkyl glycoside. In some embodiments, the at least one alkyl glycoside is one described in United States Patent No. 5,661,130~~, which is incorporated by reference herein~~.

~~[052]~~[047] In some embodiments, the composition comprises a benzodiazepine drug that is fully dissolved in a solvent comprising a natural or synthetic tocopherol or tocotrienol, and an alcohol or glycol. In some embodiments, the composition comprises a benzodiazepine drug that is fully dissolved in a solvent comprising a natural or synthetic tocopherol or tocotrienol and ~~an~~ said alcohol~~s or glycol~~, wherein the solution is at least substantially free of water. (In some embodiments, "substantially free of water" indicates that the solution contains less than about 1%, less than about 0.5%, less than about 0.25% or less than about 0.1% water.) In some embodiments, the composition consists essentially of a benzodiazepine drug that is fully dissolved in a solvent consisting of one or more natural or synthetic tocopherols or tocotrienols, one or more alcohols or glycols, and ~~optionally~~ one or more alkyl glycosides as defined in the claims. In some embodiments, the composition consists essentially of a benzodiazepine drug that is fully dissolved in a solvent consisting of one or more natural or synthetic tocopherols or tocotrienols, one or more alcohols or glycols, and optionally one or more alkyl glycosides as defined in the claims wherein the solution is at least substantially free of water. (In some embodiments, "substantially free of water" indicates that the solution contains less than about 1%, less than about 0.5%, less than about 0.25% or less than about 0.1% water.) In some embodiments, the composition consists of a benzodiazepine dissolved in a solvent consisting of one or more natural or synthetic tocopherols or tocotrienols, one or more alcohols or glycols, and ~~optionally~~ one or more alkyl glycosides as defined in the claims. In some embodiments, the composition consists of a benzodiazepine dissolved in a solvent consisting of one or more natural or synthetic tocopherols or tocotrienols, one or more alcohols or glycols, and ~~optionally~~ one or more alkyl glycosides as defined in the claims, wherein the solution is at least substantially free of water. (In some embodiments, "substantially free of water" indicates that the solution contains less than about 1%, less than about 0.5%, less than about 0.25% or less than about 0.1% water.)

~~[053]~~[048] In some embodiments, the composition comprises a benzodiazepine drug that is fully dissolved in a solvent comprising a natural or synthetic tocopherol or tocotrienol, and an alcohol or glycol as

defined in the claims. Thus, in some embodiments, the composition is substantially free of benzodiazepine microparticles, nanoparticles or combinations thereof. In some embodiments, the composition comprises a benzodiazepine drug that is fully dissolved in a solvent comprising a natural or synthetic tocopherol or tocotrienol and an alcohol or glycol as defined in the claims, wherein the solution is at least substantially free of water. (In some embodiments, "substantially free of water" indicates that the solution contains less than about 1%, less than about 0.5%, less than about 0.25% or less than about 0.1% water.) In some embodiments, the composition consists essentially of a benzodiazepine drug that is fully dissolved in a solvent consisting of one or more natural or synthetic tocopherols or tocotrienols, one or more alcohols or glycols, and ~~optionally~~ one or more alkyl glycosides as defined in the claims. In some embodiments, the composition consists essentially of a benzodiazepine drug that is fully dissolved in a solvent consisting of one or more natural or synthetic tocopherols or tocotrienols, one or more alcohols or glycols, and ~~optionally~~ one or more alkyl glycosides as defined in the claims wherein the solution is at least substantially free of water. (In some embodiments, "substantially free of water" indicates that the solution contains less than about 1%, less than about 0.5%, less than about 0.25% or less than about 0.1% water.) In some embodiments, the composition consists of a benzodiazepine dissolved in a solvent consisting of one or more natural or synthetic tocopherols, one or more alcohols or glycols, and ~~optionally~~ one or more alkyl glycosides as defined in the claims. In some embodiments, the composition consists of a benzodiazepine dissolved in a solvent consisting of one or more natural or synthetic tocopherols, one or more alcohols or glycols, and ~~optionally~~ one or more alkyl glycosides as defined in the claims, wherein the solution is at least substantially free of water. (In some embodiments, "substantially free of water" indicates that the solution contains less than about 1%, less than about 0.5%, less than about 0.25% or less than about 0.1% water.)

~~[054] In some embodiments, the~~Disclosed is a composition which contains a benzodiazepine drug that at least partially in a particulate form suspended in a carrier system containing a natural or synthetic tocopherol or tocotrienol and one or more alcohols or glycols. ~~In some embodiments,~~Disclosed is that substantially all the benzodiazepine drug is in a particulate form. ~~In some embodiments~~Disclosed is that ~~,~~ at least part of the benzodiazepine drug is in a microparticulate or nanoparticulate form. The carrier system is one in which the amount of at least one benzodiazepine present in the composition exceeds its solubility in the carrier system. ~~In some embodiments, a~~A carrier system in such a composition can include~~s~~ water. ~~In some embodiments, s~~Such a liquid carrier system can contain~~s~~ water and one or more excipients. ~~In some embodiments, o~~One or more excipients ~~are~~ can be dissolved or suspended in the carrier system. ~~In some embodiments, a~~~~At least one such excipient can stabilizes the suspension of benzodiazepine particulates in the carrier system. In some embodiments, t~~The carrier system may contain varying concentrations of parabens (e.g. methylparaben, propylparaben, etc.), and/or varying amounts of one or more surfactants, such as povidone (polyvinyl pyrrolidinone). ~~In some embodiments, b~~Benzodiazepine particulate suspensions can specifically exclude one or more polymeric glycols, such as polyethylene glycol. ~~In some embodiments, b~~Benzodiazepine particulate suspensions can specifically exclude one or more polymeric glycols having a molecular weight greater than about 200 g/mol. ~~In some embodiments, t~~The composition can comprises a benzodiazepine drug in a form

including benzodiazepine microparticles and/or nanoparticles suspended in a carrier system comprising synthetic tocopherol, one or more parabens, one or more alcohols or glycols, one or more surfactants and water. ~~In some embodiments, tThe composition can comprises a benzodiazepine drug in a form including benzodiazepine microparticles or nanoparticles suspended in a carrier system comprising Vitamin E TPGS, one or both of methylparaben and propylparaben, at least one glycol, povidone and water. In some embodiments, Tthe composition can comprises a benzodiazepine drug in a form including benzodiazepine microparticles and/or nanoparticles suspended in a carrier system comprising Vitamin E TPGS, methylparaben, propylparaben, propylene glycol, povidone and water. In some embodiments, t~~The composition can consists essentially of a benzodiazepine drug in a form including benzodiazepine microparticles and/or nanoparticles suspended in a carrier system consisting essentially of a synthetic tocopherol, one or more parabens, one or more alcohols or glycols, one or more surfactants and water. ~~In some embodiments, thThe composition can consists essentially of a benzodiazepine drug in a form including benzodiazepine microparticles or nanoparticles suspended in a carrier system consisting essentially of Vitamin E TPGS, one or both of methylparaben and propylparaben, at least one glycol, povidone and water. In some embodiments, tThe composition can consists essentially of a benzodiazepine drug in a form including benzodiazepine microparticles and/or nanoparticles suspended in a carrier system consisting essentially of Vitamin E TPGS, methylparaben, propylparaben, propylene glycol, povidone and water. In some embodiments, t~~The composition can consist~~s~~ of a benzodiazepine drug in a form including benzodiazepine microparticles and/or nanoparticles suspended in a carrier system consisting of a synthetic tocopherol, one or more parabens, one or more alcohols or glycols, one or more surfactants and water. ~~In some embodiments, Tthe composition can consists of a benzodiazepine drug in a form including benzodiazepine microparticles or nanoparticles suspended in a carrier system consisting of Vitamin E TPGS, one or both of methylparaben and propylparaben, at least one glycol, povidone and water. In some embodiments, tThe composition can consists of a benzodiazepine drug in a form including benzodiazepine microparticles and/or nanoparticles suspended in a carrier system consisting of Vitamin E TPGS, methylparaben, propylparaben, propylene glycol, povidone and water.~~

~~[055]~~[049] ~~In some embodiments,~~Disclosed is a ~~the~~ composition which contains a benzodiazepine drug that at least partially in a particulate form suspended in a carrier system containing a natural or synthetic tocopherol or tocotrienol, one or more alcohols or glycols, and an alkyl glycoside. ~~In some embodiments, s~~Substantially all the benzodiazepine drug ~~is~~ can be in a particulate form. ~~In some embodiments, a~~At least part of the benzodiazepine drug is in a microparticulate or nanoparticulate form. The carrier system is one in which the amount of at least one benzodiazepine present in the composition exceeds its solubility in the carrier system. ~~In some embodiments, a~~A carrier system in such a composition can include~~s~~ water. ~~In some embodiments, s~~Such a liquid carrier system can contain~~s~~ water and one or more excipients. ~~In some embodiments, o~~One or more excipients ~~are~~ can be dissolved or suspended in the carrier system. ~~In some embodiments, a~~At least one such excipient can stabilize~~s~~ the suspension of benzodiazepine particulates in the carrier system. ~~In some embodiments, tThe carrier system may contain varying concentrations of parabens~~

~~(e.g. methylparaben, propylparaben, etc.), and/or varying amounts of one or more surfactants, such as povidone (polyvinyl pyrrolidinone). In some embodiments, b~~Benzodiazepine particulate suspensions can specifically exclude one or more polymeric glycols, such as polyethylene glycol. ~~In some embodiments, b~~Benzodiazepine particulate suspensions can specifically exclude one or more polymeric glycols having a molecular weight greater than about 200 g/mol. ~~In some embodiments, t~~The composition can comprise~~s~~ a benzodiazepine drug in a form including benzodiazepine microparticles and/or nanoparticles suspended in a carrier system comprising a synthetic tocopherol, one or more parabens, one or more alcohols or glycols, an alkyglycoside and water. ~~In some embodiments, tThe composition can comprises a benzodiazepine drug in a form including benzodiazepine microparticles or nanoparticles suspended in a carrier system comprising Vitamin E TPGS, one or both of methylparaben and propylparaben, at least one glycol, an alkyl glycoside and water. In some embodiments, tThe composition can comprises a benzodiazepine drug in a form including benzodiazepine microparticles and/or nanoparticles suspended in a carrier system comprising Vitamin E TPGS, methylparaben, propylparaben, propylene glycol, an alkyl glycoside and water. In some embodiments, t~~The composition consists essentially of a benzodiazepine drug in a form including benzodiazepine microparticles and/or nanoparticles suspended in a carrier system consisting essentially of a synthetic tocopherol, one or more parabens, one or more alcohols or glycols, an alkyl glycoside, optionally a surfactant, and water. ~~In some embodiments, tThe composition can consists essentially of a benzodiazepine drug in a form including benzodiazepine microparticles or nanoparticles suspended in a carrier system consisting essentially of Vitamin E TPGS, one or both of methylparaben and propylparaben, at least one glycol, an alkyl glycoside, optionally a povidone and water. In some embodiments, tThe composition can consists essentially of a benzodiazepine drug in a form including benzodiazepine microparticles and/or nanoparticles suspended in a carrier system consisting essentially of Vitamin E TPGS, methylparaben, propylparaben, propylene glycol, an alkyl glycoside, optionally a povidone, and water. In some embodiments, t~~The composition can consist~~s~~ of a benzodiazepine drug in a form including benzodiazepine microparticles and/or nanoparticles suspended in a carrier system consisting of a synthetic tocopherol, one or more parabens, one or more alcohols or glycols, an alkyl glycoside, optionally one or more surfactants, and water. ~~In some embodiments, tThe composition can consists of a benzodiazepine drug in a form including benzodiazepine microparticles or nanoparticles suspended in a carrier system consisting of Vitamin E TPGS, one or both of methylparaben and propylparaben, at least one glycol, an alkyl glycoside, optionally a povidone and water. In some embodiments, tThe composition can consists of a benzodiazepine drug in a form including benzodiazepine microparticles and/or nanoparticles suspended in a carrier system consisting of Vitamin E TPGS, methylparaben, propylparaben, propylene glycol, an alkyl glycoside, optionally a povidone and water.~~

~~[056]~~[050] The invention also discloses a method of treating a patient with a disorder that may be treatable with a benzodiazepine drug. In some embodiments, the patient is a human. In some embodiments, the method comprises: administering to one or more nasal mucosal membranes of a patient a pharmaceutical composition for nasal administration ~~comprising a benzodiazepine drug; one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w);~~

(markup)

~~and one or more alcohols or glycols, or any combinations thereof, in an amount from about 5% to about 70% (w/w), preferably about 10% to about 70% (w/w). In some embodiments, the benzodiazepine is dissolved in the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); and the one or more alcohols or glycols, or any combinations thereof, in an amount from about 5% to about 70% (w/w), preferably about 10% to about 70% (w/w). In some embodiments, the benzodiazepine drug is dissolved in a carrier system. In other embodiments, at least part of the benzodiazepine drug is in a form including microparticles, nanoparticles, or combinations thereof. In some embodiments, the composition is substantially free of benzodiazepine microparticles, nanoparticles or combinations thereof~~as defined in the claims.

~~[057]~~[051] In some embodiments, the benzodiazepine drug is selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, or any pharmaceutically-acceptable salts thereof, and any combinations thereof. In some embodiments, the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof. In some embodiments, the benzodiazepine drug comprises benzodiazepine microparticles, nanoparticles, or combinations thereof. In some embodiments, the benzodiazepine nanoparticles have an effective average particle size of less than about 5000 nm.

~~[058]~~[052] In some embodiments, the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ- tocotrienol, δ-tocotrienol, tocophersolan, any isomers thereof, any esters thereof, any analogs or derivatives thereof, and any combinations thereof. A synthetic tocopherol may include a tocopherol that has been modified to include a hydrophilic group, such as a polyethylene glycol group, which may be directly covalently bonded to the tocopherol or may be linked to the tocopherol through a covalent linking group, such as a diacid. An exemplary synthetic tocopherol of this type is Vitamin E Polyethylene Glycol Succinate (Vitamin E TPGS), although the person skilled in the art will be able to envision other synthetic tocopherols that have similar diacid and/or hydrophilic groups.

~~[059]~~[053] ~~In some embodiments, the one or more alcohols are selected from the group consisting of: ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, and any combinations thereof.~~ In some embodiments, ~~the~~ one or more glycols are present as excipients and are selected from the group consisting of: ethylene glycol, propylene glycol, butylene glycol, pentylene glycol, any isomers thereof, and any combinations thereof. In some embodiments, one or more glycols specifically excludes polymeric glycols, such as polyethylene glycol. In some embodiments, one or more glycols specifically excludes a polymeric glycol having a molecular weight of greater than about 200 g/mol.

~~[060]~~[054] In some embodiments, the benzodiazepine drug is present in the carrier system in a concentration from about 1 mg/mL to about 600 mg/mL. In some embodiments, the benzodiazepine drug is present in the carrier system in a concentration of from about 10 mg/mL to about 250 mg/mL. In some

embodiments, the benzodiazepine drug is present in the carrier system in a concentration of from about 20 mg/mL to about 50 mg/mL.

~~[061]~~[055] In some embodiments, the carrier system comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 45% to about 85% (w/w). In some embodiments, the carrier system comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 60% to about 75% (w/w). In some embodiments, the carrier system comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount of about 70% (w/w). In some embodiments, especially where particulate suspensions of a benzodiazepine drug are contemplated, the compositions may include a tocopherol, especially a synthetic tocopherol having a hydrophilic group covalently linked to a tocopherol. In other embodiments, especially where a solution of benzodiazepine drug is contemplated, the tocopherol is substantially or completely free of Vitamin E TPGS.

~~[062] In some embodiments, the carrier system comprises one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 55% (w/w). In some embodiments, the carrier system comprises one or more alcohols or glycols, or any combinations thereof, in an amount from about 25% to about 40% (w/w). In some embodiments, the carrier system comprises one or more alcohols or glycols, or any combinations thereof, in an amount from about 30% (w/w). In some embodiments the amount of one or more alcohols or glycols in the carrier system is about 10% to about 55%, about 10% to about 40%, about 10% to about 35%, about 12% to about 55%, about 12% to about 40%, about 12% to about 35%, about 15% to about 55%, about 15% to about 40%, about 15% to about 35%, about 10%, about 12.5%, about 15%, about 17.5%, about 20%, about 22.5%, about 25%, about 27.5%, about 30%, about 32.5%, about 35%, about 37.5%, about 40%, about 42.5%, about 45%, about 47.5%, about 50%, about 52.5% or about 55% (w/w).~~

~~[063]~~[056] In some embodiments, the composition comprises at least one additional ingredient selected from the group consisting of: active pharmaceutical ingredients; enhancers; excipients; and agents used to adjust the pH, buffer the composition, prevent degradation, and improve appearance, odor, or taste.

~~[064]~~[057] In some embodiments, a composition comprises at least one penetration enhancer in addition to a benzodiazepine drug, a natural or synthetic tocopherol or tocotrienol, and an alcohol or glycol. In some embodiments, the penetration enhancer is an alkyl glycoside. In some embodiments, the alkyl glycoside refers to any sugar joined to any hydrophobic alkyl, as described in United States patent number 5,661,130~~, which is incorporated herein by reference in its entirety~~. The hydrophobic alkyl can be any suitable length, for example about 9 to about 24 carbons in length, especially about 10 to about 14 carbons in length. The hydrophobic alkyl can be branched and/or partially or wholly unsaturated. The alkyl may be joined to the saccharide core for example through a carbonyl group, whereby an ester group may be formed. A suitable alkyl glycoside will have the characteristics of being nontoxic, nonionic, and capable of increasing the absorption of a benzodiazepine drug when it is administered intranasally as described herein. Exemplary saccharides that may be covalently joined to an alkyl according to the present invention include glucose, maltose, maltotriose, maltotetrose, sucrose and trehalose. Exemplary alkyl glycosides that may be employed include octyl-, nonyl-,

decyl-, undecyl-, dodecyl, tridecyl, tetradecyl, pentadecyl, octadecyl α- or β-D-maltoside, -glucoside or sucroside. In some embodiments, the preferred glycosides include maltose, sucrose or glucose linked by glycosidic linkage to an alkyl chain of 9, 10, 12, 14, 16, 18 or 20 carbon atoms. Where present, the amount of alkyl glycoside in the composition is sufficient to enhance the absorption of a benzodiazepine drug administered by the intranasal route. In some embodiments, the amount of alkyl glycoside in the composition is selected so as to enhance absorption of the benzodiazepine drug, while at the same time not significantly irritating the nasal mucosa. In some embodiments, the amount of alkyl glycoside in the composition is in a range of about 0.01% (w/v) to about 1% (w/v). In some embodiments, the amount of alkyl glycoside in the composition is in a range of about 0.05% (w/v) to about 0.5% (w/v), or about 0.125% (w/v) to about 0.5% (w/v).

~~[065]~~[058] In some embodiments, the composition is in a pharmaceutically-acceptable spray formulation, and further comprising administering the composition to one or more nasal mucosal membranes of the patient. In some embodiments, the therapeutically effective amount is from about 1 mg to about 20 mg of the benzodiazepine. In some embodiments, the pharmaceutical composition is in a pharmaceutically-acceptable spray formulation having volume from about 10 μL to 200 μL.

~~[066]~~[059] In some embodiments, the administration of the composition comprises spraying at least a portion of the therapeutically effective amount of the composition into at least one nostril. In some embodiments, the administration of the composition comprises spraying at least a portion of the therapeutically effective amount of the composition into each nostril. In some embodiments, the administration of the composition comprises spraying a first quantity of the composition into the first nostril, spraying a second quantity of the composition into a second nostril, and optionally after a pre-selected time delay, spraying a third quantity of the composition into the first nostril. Some embodiments further comprise, optionally after a pre-selected time delay, administering at least a fourth quantity of the composition to the second nostril.

~~[067]~~[060] In some embodiments, the administration of the composition begins at any time before or after onset of symptoms of a disorder which may be treatable with the composition.

Definitions

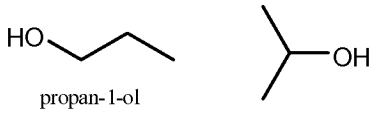
~~[068]~~[061] As used herein the phrase “therapeutically effective amount” (or more simply “effective amount”) includes an amount sufficient to provide a specific therapeutic response for which the drug is administered to a patient in need of particular treatment. The skilled clinician will recognize that the therapeutically effective amount of drug will depend upon the patient, the indication and the particular drug administered.

~~[069]~~[062] As used herein, the modifier “about” is intended to have its regularly recognized meaning of approximately. In some embodiments, the term may be more precisely interpreted as meaning within a

particular percentage of the modified value, e.g. "about" may in some embodiments mean ± 20%, ± 10%, ± 5%, ± 2%, or ± 1% or less.

~~[070]~~[063] As used herein, the phrase "analogs or derivatives" includes molecules that differ from one another molecule due to one or more atoms or functional groups having been replaced with a different atom or functional group. This may result in molecules with similar chemical formulas but different chemical and/or biological properties.

~~[071]~~[064] As used herein, the term, "isomer" includes molecules with identical chemical formulas, but between which the arrangement of the molecules may vary. These varying arrangements may result in molecules with identical chemical formulas but different chemical properties. By way of non-limiting example, propanol has the chemical formula C_3H_7OH. It may be found as propan-1-ol, wherein the –OH is found attached to an end carbon. Alternatively, it may be found as propan-2-ol, wherein the –OH is found attached to the second carbon.



propan-1-ol propan-2-ol

~~[072]~~[065] As used herein, the term "seizure" includes commonly recognized types of seizures, including absence seizures, myoclonic seizures, clonic seizures, tonic seizures, tonic-clonic seizures, and atonic seizures. Often seizures, particularly severe tonic or tonic-clonic seizures, will be presaged by one or more aura that will be familiar to the patient or those familiar with the patient. Each patient will generally experience a different type of aura, which is unique to the patient; however auras may be classified as audible, visual, olfactory or tactile sensations that usually, or at least often, precedes a patient's experiencing a seizure. (Not all patients who suffer seizures experience aura; however aura are not uncommon amongst those who suffer the worst type of seizures, especially tonic-clonic seizures.)

~~[073]~~[066] As used herein, the term "prevention" refers to a forestalling, including temporary forestalling, of the onset of a disorder. In the case of seizures, this can occur either with or without the benefit of a warning aura.

~~[074]~~[067] As used herein, the term "treatment" refers to a reduction in the intensity and/or duration of a disorder, or similar effects. The term also encompasses the side-effects of such a "treatment."

~~[075]~~[068] As used herein, unless otherwise qualified, "a" and "an" can mean one or more.

~~[076]~~[069] As used herein, the term "comprising" in all its variants, is a transitional phrase used in a claim to indicate that the invention includes or contains, but is not limited to, the specifically recited claim elements.

~~[077]~~[070] As used herein, the phrase "consisting essentially of" is a transitional phrase used in a claim to indicate that the a following list of ingredients, parts or process steps must be present in the claimed composition, machine or process, but that the claim is open to unlisted ingredients, parts or process steps that do not materially affect the basic and novel properties of the invention.

(markup)

~~[078]~~[071] As used herein, the term "consisting of" is a transitional phrase used in a claim to indicate that the claimed invention includes only those elements set forth in the claim.

Benzodiazepine Drugs

~~[079]~~[072] In the context of the present invention, the term "benzodiazepine drug" includes any therapeutically effective benzodiazepine compound, or pharmaceutically acceptable salt, or combinations thereof. In some embodiments, benzodiazepine comprises a member of the group consisting of alprazolam, diazepam, flurazepam, lorazepam, medazepam, mexazolam, midazolam, temazepam and pharmaceutically acceptable salts and combinations thereof.

~~[080]~~[073] It should be recognized by those of skill in the art that additional benzodiazepine compounds that have heretofore been considered to have marginal or little therapeutic benefit, either because of low bioavailability, poor pharmacokinetic properties or poor pharmacodynamic properties, may find use through the present invention, which can provide for improved bioavailability of benzodiazepine drugs, delivery of higher concentrations of benzodiazepine drugs via the nasal route, faster attainment of therapeutic levels of benzodiazepine in the blood plasma, avoidance of the liver portal vein and concomitant avoidance of first pass effects and/or faster presentation of benzodiazepine drug to the brain.

~~[081]~~[074] For example, most benzodiazepines are so slightly soluble in water that a therapeutically effective amount cannot be dissolved in a volume of aqueous solvent that is amenable to application to a mucosal membrane. By use of the present carrier system, which in some embodiments, provides an improved ability to dissolve benzodiazepine drugs, the present invention allows benzodiazepine drugs to be administered to one or more mucosal membranes, including to nasal mucosal membranes. This can allow one to administer the drug without hospitalization or unnecessary discomfort. Additionally, in some embodiments of the present invention, such as nasal administration, the digestive system largely may be bypassed. This latter improvement can yield improved bioavailability, faster attainment of therapeutic levels of benzodiazepine in the blood plasma, avoidance of the liver portal vein, and/or concomitant avoidance of first pass effects.

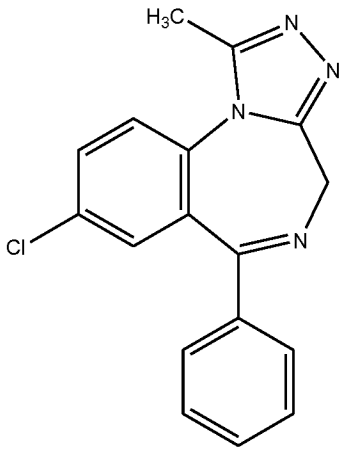
~~[082]~~[075] Nasal administration of the composition can result in faster presentation of the one or more benzodiazepine drugs to the brain due to the close proximity of the membranes and the brain. A seizing patient, for example, suffers from rigid muscles and uncontrollable movement. This can make oral and/or intravenous administration difficult or inconvenient. However, the nasal passageways remain open and easily accessible, and therefore is a useful route of administration for of the present invention.

~~[083]~~[076] In some embodiments, the pharmaceutical composition is used as defined in the claims to treat a patient suffering from a disorder that is amenable to treatment or prevention with an effective amount of the one or more benzodiazepine drugs. By way of non-limiting example such disorders can include: insomnia, anxiety, seizures, muscle spasms and rigidity, and the symptoms of drug withdrawal.

~~[084]~~[077] In some embodiments, the one or more benzodiazepine drugs, are used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the

intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure.

~~[085]~~[078] **Alprazolam** (8-chloro-6-phenyl-1-methyl-4H-1,2,4-triazolo[4,3-a][1,4]benzodiazepine).



~~[086]~~[079] Alprazolam is a benzodiazepine drug having sedative, tranquilizing and muscle relaxing properties. It is classified as an anxiolytic. Alprazolam has also been shown to be useful in the treatment of panic disorder. The dosage of alprazolam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.5 to about 4, preferably about 1 to about 2 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Alprazolam may be manufactured using the process disclosed in United States patent 3,987,052~~, which is incorporated herein by reference in its entirety~~.

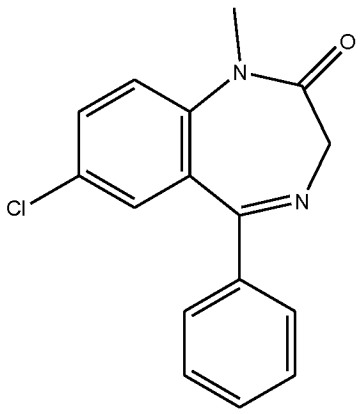
~~[087]~~[080] In some embodiments, alprazolam is used alone or in combination with other drugs to provide an anxiolytic effect, an anticonvulsant effect, a sedative effect, a skeletal muscle relaxant effect, an amnesic effect or combinations of the foregoing effects.

~~[088]~~[081] In some embodiments, alprazolam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Alprazolam may be administered by the patient or other person (such as a healthcare professional) while the patient is in a non-seizing state to protect against seizure. Even where protection against seizure is not absolute, administration of alprazolam may reduce or ameliorate the intensity of seizure and/or reduce or ameliorate the frequency of seizure. In some embodiments, administration of alprazolam may prevent occurrence of seizure. In some embodiments, especially where the patient is prone to experiencing serial seizures or *status epilepticus*, administration of alprazolam may aid in interrupting the seizure cycle and may thus prevent the re-occurrence of seizure. In addition to the benzodiazepines (such as diazepam), other anti-convulsant drugs may be combined with alprazolam to provide an anticonvulsant or synergistic anticonvulsant effect.

~~[089]~~[082] Alprazolam may also be administered by another person (*e.g.* an acquaintance or associate, a family member or a health care professional) to the patient while the patient is in a state of seizure. Thus, one of the advantages of the formulations for use according to the present invention is the ability to administer them in an acute therapeutic environment to treat the seizure victim, for example, nasally. Among the beneficial therapeutic effects that may be imparted by acute dosing of benzodiazepine anticonvulsants, such as nasal dosing, are: reduction in the severity of the seizure (*e.g.* general relaxation of the muscles, reduction in seizure-induced anxiety experienced by the patient and a general impartation of a feeling of well-being to the patient), reduction in the duration of the seizure, reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between the current seizure and the next seizure. Thus, the alprazolam formulations of the invention, and in particular nasal formulations, provide fast onset of therapeutic benefit – in some instances less than about 30 minutes, less than about 15 minutes, less than about 10 minutes, and in some cases less than about 5 minutes. The alprazolam formulations of the invention, and in particular nasal formulations, also provide convenient administration of a therapeutically beneficial drug to a patient that does not require intravenous drug administration or rectal drug administration.

~~[090]~~[083] Often seizures, particularly severe tonic or tonic-clonic seizures, will be presaged by one or more aura events that will be familiar to the patient or those familiar with the patient. These auras are practically *sui generis* for each patient, but may be classified as audible, visual, olfactory or tactile sensations that usually, or typically, precedes a patient's experiencing a seizure. In some embodiments of the invention, the method includes prompt administration of a preparation of a benzodiazepine drug according to the invention during the aura. In some embodiments, such intra-aural administration of benzodiazepine drug, for example by nasal administration, will prevent or at least ameliorate the effects (intensity, duration or both) of the impending seizure. Thus, in the context of this invention, prevention of seizure refers to a temporary forestalling of the onset of seizure, either with or without the benefit of a warning aura.

~~[091]~~[084] **Diazepam** (7-chloro-1-methyl-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one)



~~[092]~~[085] Diazepam is a benzodiazepine drug having sedative, tranquilizing and muscle relaxing properties. It is classified as an anxiolytic and skeletal muscle relaxant. It possesses anxiolytic, anticonvulsant, sedative, skeletal muscle relaxant and amnesic properties. The dosage of diazepam may vary by indication, however it is expected that a therapeutic dose will be in the range of about 1 to about 20, preferably about 2 to

about 10 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Diazepam may be manufactured using the process disclosed in one of United States patents 3,371,085; 3,109,843; 3,136,815 or 3,102,116~~, each of which is incorporated herein by reference in its entirety~~.

~~[093]~~[086] In some embodiments, diazepam is used alone or in combination with other drugs to provide an anxiolytic effect, an anticonvulsant effect, a sedative effect, a skeletal muscle relaxant effect, an amnesic effect or combinations of the foregoing effects.

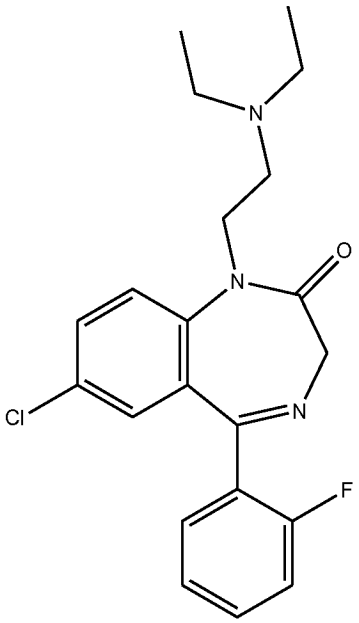
~~[094]~~[087] In some embodiments, diazepam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Diazepam may be administered by the patient or other person (such as a healthcare professional) while the patient is in a non-seizing state to protect against seizure. Even where protection against seizure is not absolute, administration of diazepam may reduce or ameliorate the intensity of seizure and/or reduce or ameliorate the frequency of seizure. In some embodiments, administration of diazepam may prevent occurrence of seizure. In some embodiments, especially where the patient is prone to experiencing serial seizures or status epilepticus, administration of diazepam may aid in interrupting the seizure cycle and may thus prevent the re-occurrence of seizure. In addition to the benzodiazepines (such as diazepam), other anti-convulsant drugs may be combined with diazepam to provide a synergistic anticonvulsant effect.

~~[095]~~[088] Diazepam may also be administered by another person (*e.g.* an acquaintance or associate, a family member or a health care professional) to the patient while the patient is in a state of seizure. Thus, one of the advantages of the formulations for use according to the present invention is the ability to administer them in an acute therapeutic environment to treat the seizure victim, for example, nasally. Among the beneficial therapeutic effects that may be imparted by acute dosing of benzodiazepine anticonvulsants, such as nasal dosing, are: reduction in the severity of the seizure (*e.g.* general relaxation of the muscles, reduction in seizure-induced anxiety experienced by the patient and a general impartation of a feeling of well-being to the patient), reduction in the duration of the seizure, reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between the current seizure and the next seizure. Thus, the diazepam formulations of the invention, and in particular nasal formulations, provide fast onset of therapeutic benefit – in some instances less than about 30 minutes, less than about 15 minutes, less than about 10 minutes, and in some cases less than about 5 minutes. The diazepam formulations of the invention, and in particular nasal formulations, also provide convenient administration of a therapeutically beneficial drug to a patient that does not require intravenous drug administration or rectal drug administration.

~~[096]~~[089] Often seizures, particularly severe tonic or tonic-clonic seizures, will be presaged by one or more aura events that will be familiar to the patient or those familiar with the patient. These auras are practically *sui generis* for each patient, but may be classified as audible, visual, olfactory or tactile sensations that usually, or typically, precedes a patient's experiencing a seizure. In some embodiments of the invention, the method includes prompt administration of a preparation of a benzodiazepine drug according to the

invention during the aura. In some embodiments, such intra-aural administration of benzodiazepine drug, for example by nasal administration, will prevent or at least ameliorate the effects (intensity, duration or both) of the impending seizure. Thus, in the context of this invention, prevention of seizure refers to a temporary forestalling of the onset of seizure, either with or without the benefit of a warning aura.

~~[097]~~[090] **Flurazepam** (7-chloro-5-(2-flurophenyl)-2,3-dihydro-1-(2-(diethylamino)ethyl)-1H-1,4-benzodiazepin-2-one)



~~[098]~~[091] Flurazepam is a benzodiazepine drug having sedative (especially soporific and hypnotic), anxiolytic, anticonvulsant and muscle relaxing properties. It is classified as an sedative, hypnotic. Flurazepam has been shown to be useful in the treatment of insomnia. The dosage of flurazepam varies by indication, however it is expected that a therapeutic dose will be in the range of about 5 to 40, preferably about 20 to about 35 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Flurazepam may be manufactured using the process disclosed in United States patent 3,567,710 or 3,299,053~~, each of which is incorporated herein by reference in its entirety~~.

~~[099]~~[092] In some embodiments, flurazepam is used alone or in combination with other drugs to provide an anxiolytic effect, an anticonvulsant effect, a sedative effect, a skeletal muscle relaxant effect, an amnesic effect or combinations of the foregoing effects.

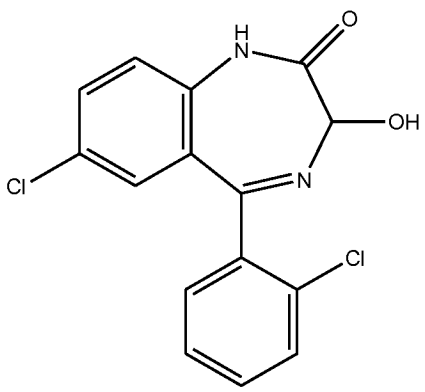
~~[0100]~~[093] In some embodiments, flurazepam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Flurazepam may be administered by the patient or other person (such as a healthcare professional) while the patient is in a non-seizing state to protect against seizure. Even where protection against seizure is not absolute, administration of flurazepam may reduce or ameliorate the intensity of seizure and/or reduce or ameliorate the frequency of seizure. In some embodiments, administration of flurazepam may prevent occurrence of seizure. In some embodiments, especially where the patient is prone to experiencing serial

seizures or status epilepticus, administration of flurazepam may aid in interrupting the seizure cycle and may thus prevent the re-occurrence of seizure. In addition to the benzodiazepines (such as diazepam), other anti-convulsant drugs may be combined with flurazepam to provide a synergistic anticonvulsant effect.

~~[0101]~~[094] Flurazepam may also be administered by another person (*e.g.* an acquaintance or associate, a family member or a health care professional) to the patient while the patient is in a state of seizure. Thus, one of the advantages of the formulations for use according to the present invention is the ability to administer them in an acute therapeutic environment to treat the seizure victim, for example, nasally. Among the beneficial therapeutic effects that may be imparted by acute dosing of benzodiazepine anticonvulsants, such as nasal dosing, are: reduction in the severity of the seizure (*e.g.* general relaxation of the muscles, reduction in seizure-induced anxiety experienced by the patient and a general impartation of a feeling of well-being to the patient), reduction in the duration of the seizure, reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between the current seizure and the next seizure. Thus, the flurazepam formulations of the invention, and in particular nasal formulations, provide fast onset of therapeutic benefit – in some instances less than about 30 minutes, less than about 15 minutes, less than about 10 minutes, and in some cases less than about 5 minutes. The flurazepam formulations of the invention, and in particular nasal formulations, also provide convenient administration of a therapeutically beneficial drug to a patient that does not require intravenous drug administration or rectal drug administration.

~~[0102]~~[095] Often seizures, particularly severe tonic or tonic-clonic seizures, will be presaged by one or more aura events that will be familiar to the patient or those familiar with the patient. These auras are practically *sui generis* for each patient, but may be classified as audible, visual, olfactory or tactile sensations that usually, or typically, precedes a patient's experiencing a seizure. In some embodiments of the invention, the method includes prompt administration of a preparation of a benzodiazepine drug according to the invention during the aura. In some embodiments, such intra-aural administration of benzodiazepine drug, for example by nasal administration, will prevent or at least ameliorate the effects (intensity, duration or both) of the impending seizure. Thus, in the context of this invention, prevention of seizure refers to a temporary forestalling of the onset of seizure, either with or without the benefit of a warning aura.

~~[0103]~~[096] **Lorazepam** (7-chloro-5-(2-chlorophenyl)-3-hydroxy-1,3-dihydro-2H-1,4-benzodiazepin-2-one)



(markup)

~~[0104]~~[097] Lorazepam is a benzodiazepine drug having sedative, tranquilizing, anticonvulsant, amnesic and muscle relaxing properties. It is classified as an anxiolytic. Lorazepam has also been shown to be useful in the treatment of nausea. The dosage of lorazepam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.1 to about 10, preferably about 0.2 to about 1 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Lorazepam may be manufactured using the process disclosed in United States patent 3,296,249~~, which is incorporated herein by reference in its entirety~~.

~~[0105]~~[098] In some embodiments, lorazepam is used alone or in combination with other drugs to provide an anxiolytic effect, an anticonvulsant effect, a sedative effect, a skeletal muscle relaxant effect, an amnesic effect or combinations of the foregoing effects.

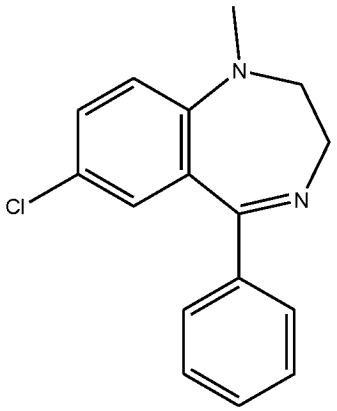
~~[0106]~~[099] In some embodiments, lorazepam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Lorazepam may be administered by the patient or other person (such as a healthcare professional) while the patient is in a non-seizing state to protect against seizure. Even where protection against seizure is not absolute, administration of lorazepam may reduce or ameliorate the intensity of seizure and/or reduce or ameliorate the frequency of seizure. In some embodiments, administration of lorazepam may prevent occurrence of seizure. In some embodiments, especially where the patient is prone to experiencing serial seizures or status epilepticus, administration of lorazepam may aid in interrupting the seizure cycle and may thus prevent the re-occurrence of seizure. In addition to the benzodiazepines (such as diazepam), other anti-convulsant drugs may be combined with lorazepam to provide a synergistic anticonvulsant effect.

~~[0107]~~[0100] Lorazepam may also be administered by another person (*e.g.* an acquaintance or associate, a family member or a health care professional) to the patient while the patient is in a state of seizure. Thus, one of the advantages of the formulations for use according to the present invention is the ability to administer them in an acute therapeutic environment to treat the seizure victim, for example, nasally. Among the beneficial therapeutic effects that may be imparted by acute dosing of benzodiazepine anticonvulsants, such as nasal dosing, are: reduction in the severity of the seizure (*e.g.* general relaxation of the muscles, reduction in seizure-induced anxiety experienced by the patient and a general impartation of a feeling of well-being to the patient), reduction in the duration of the seizure, reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between the current seizure and the next seizure. Thus, the lorazepam formulations of the invention, and in particular nasal formulations, provide fast onset of therapeutic benefit – in some instances less than about 30 minutes, less than about 15 minutes, less than about 10 minutes, and in some cases less than about 5 minutes. The lorazepam formulations of the invention, and in particular nasal formulations, also provide convenient administration of a therapeutically beneficial drug to a patient that does not require intravenous drug administration or rectal drug administration.

~~[0108]~~[0101] Often seizures, particularly severe tonic or tonic-clonic seizures, will be presaged by one or more aura events that will be familiar to the patient or those familiar with the patient. These auras are

practically *sui generis* for each patient, but may be classified as audible, visual, olfactory or tactile sensations that usually, or typically, precedes a patient's experiencing a seizure. In some embodiments of the invention, the method includes prompt administration of a preparation of a benzodiazepine drug according to the invention during the aura. In some embodiments, such intra-aural administration of benzodiazepine drug, for example by nasal administration, will prevent or at least ameliorate the effects (intensity, duration or both) of the impending seizure. Thus, in the context of this invention, prevention of seizure refers to a temporary forestalling of the onset of seizure, either with or without the benefit of a warning aura.

~~[0109]~~[0102] **Medazepam** ((7-chloro-1-methyl-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepine)



~~[0110]~~[0103] Medazepam is a benzodiazepine drug having sedative, tranquilizing, anticonvulsant, amnesic and muscle relaxing properties. It is classified as an anxiolytic. Medazepam has also been shown to be useful in the treatment of nausea. The dosage of medazepam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.1 to about 10, preferably about 0.2 to about 1 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Medazepam may be manufactured using the process disclosed in United States patent 3,243,427~~, which is incorporated herein by reference in its entirety~~.

~~[0111]~~[0104] In some embodiments, medazepam is used alone or in combination with other drugs to provide an anxiolytic effect, an anticonvulsant effect, a sedative effect, a skeletal muscle relaxant effect, an amnesic effect or combinations of the foregoing effects.

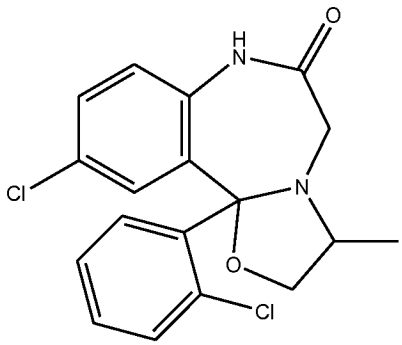
~~[0112]~~[0105] In some embodiments, medazepam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Medazepam may be administered by the patient or other person (such as a healthcare professional) while the patient is in a non-seizing state to protect against seizure. Even where protection against seizure is not absolute, administration of medazepam may reduce or ameliorate the intensity of seizure and/or reduce or ameliorate the frequency of seizure. In some embodiments, administration of medazepam may prevent occurrence of seizure. In some embodiments, especially where the patient is prone to experiencing serial seizures or status epilepticus, administration of medazepam may aid in interrupting the seizure cycle and may

thus prevent the re-occurrence of seizure. In addition to the benzodiazepines (such as diazepam), other anti-convulsant drugs may be combined with medazepam to provide a synergistic anticonvulsant effect.

~~[0113]~~[0106] Medazepam may also be administered by another person (*e.g.* an acquaintance or associate, a family member or a health care professional) to the patient while the patient is in a state of seizure. Thus, one of the advantages of the formulations for use according to the present invention is the ability to administer them in an acute therapeutic environment to treat the seizure victim, for example, nasally. Among the beneficial therapeutic effects that may be imparted by acute dosing of benzodiazepine anticonvulsants, such as nasal dosing, are: reduction in the severity of the seizure (*e.g.* general relaxation of the muscles, reduction in seizure-induced anxiety experienced by the patient and a general impartation of a feeling of well-being to the patient), reduction in the duration of the seizure, reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between the current seizure and the next seizure. Thus, the medazepam formulations of the invention, and in particular nasal formulations, provide fast onset of therapeutic benefit – in some instances less than about 30 minutes, less than about 15 minutes, less than about 10 minutes, and in some cases less than about 5 minutes. The medazepam formulations of the invention, and in particular nasal formulations, also provide convenient administration of a therapeutically beneficial drug to a patient that does not require intravenous drug administration or rectal drug administration.

~~[0114]~~[0107] Often seizures, particularly severe tonic or tonic-clonic seizures, will be presaged by one or more aura events that will be familiar to the patient or those familiar with the patient. These auras are practically *sui generis* for each patient, but may be classified as audible, visual, olfactory or tactile sensations that usually, or typically, precedes a patient's experiencing a seizure. In some embodiments of the invention, the method includes prompt administration of a preparation of a benzodiazepine drug according to the invention during the aura. In some embodiments, such intra-aural administration of benzodiazepine drug, for example by nasal administration, will prevent or at least ameliorate the effects (intensity, duration or both) of the impending seizure. Thus, in the context of this invention, prevention of seizure refers to a temporary forestalling of the onset of seizure, either with or without the benefit of a warning aura.

~~[0115]~~[0108] **Mexazolam** (10-Chloro-11b-(2-chlorophenyl)-1,3,7,11b-tetrahydro-3-methyloxazolo[3,2-d][1,4]benzodiazepin-6(5H)-one)



~~[0116]~~[0109] Mexazolam is a benzodiazepine drug having sedative, tranquilizing, anticonvulsant, amnesic and muscle relaxing properties. It is classified as an anxiolytic. Mexazolam has also been shown to be useful

in the treatment of nausea. The dosage of mexazolam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.1 to about 10, preferably about 0.2 to about 1 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Mexazolam may be manufactured using the process disclosed in United States patent 3,722,371~~, which is incorporated herein by reference in its entirety~~.

~~[0117]~~[0110] In some embodiments, mexazolam is used alone or in combination with other drugs to provide an anxiolytic effect, an anticonvulsant effect, a sedative effect, a skeletal muscle relaxant effect, an amnesic effect or combinations of the foregoing effects.

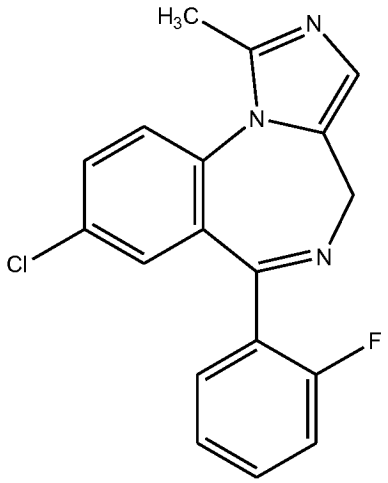
~~[0118]~~[0111] In some embodiments, mexazolam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Mexazolam may be administered by the patient or other person (such as a healthcare professional) while the patient is in a non-seizing state to protect against seizure. Even where protection against seizure is not absolute, administration of mexazolam may reduce or ameliorate the intensity of seizure and/or reduce or ameliorate the frequency of seizure. In some embodiments, administration of mexazolam may prevent occurrence of seizure. In some embodiments, especially where the patient is prone to experiencing serial seizures or status epilepticus, administration of mexazolam may aid in interrupting the seizure cycle and may thus prevent the re-occurrence of seizure. In addition to the benzodiazepines (such as diazepam), other anti-convulsant drugs may be combined with mexazolam to provide a synergistic anticonvulsant effect.

~~[0119]~~[0112] Mexazolam may also be administered by another person (*e.g.* an acquaintance or associate, a family member or a health care professional) to the patient while the patient is in a state of seizure. Thus, one of the advantages of the formulations for use according to the present invention is the ability to administer them in an acute therapeutic environment to treat the seizure victim, for example, nasally. Among the beneficial therapeutic effects that may be imparted by acute dosing of benzodiazepine anticonvulsants, such as nasal dosing, are: reduction in the severity of the seizure (*e.g.* general relaxation of the muscles, reduction in seizure-induced anxiety experienced by the patient and a general impartation of a feeling of well-being to the patient), reduction in the duration of the seizure, reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between the current seizure and the next seizure. Thus, the mexazolam formulations of the invention, and in particular nasal formulations, provide fast onset of therapeutic benefit – in some instances less than about 30 minutes, less than about 15 minutes, less than about 10 minutes, and in some cases less than about 5 minutes. The mexazolam formulations of the invention, and in particular nasal formulations, also provide convenient administration of a therapeutically beneficial drug to a patient that does not require intravenous drug administration or rectal drug administration.

~~[0120]~~[0113] Often seizures, particularly severe tonic or tonic-clonic seizures, will be presaged by one or more aura events that will be familiar to the patient or those familiar with the patient. These auras are practically *sui generis* for each patient, but may be classified as audible, visual, olfactory or tactile sensations that usually, or typically, precedes a patient's experiencing a seizure. In some embodiments of the invention,

the method includes prompt administration of a preparation of a benzodiazepine drug according to the invention during the aura. In some embodiments, such intra-aural administration of benzodiazepine drug, for example by nasal administration, will prevent or at least ameliorate the effects (intensity, duration or both) of the impending seizure. Thus, in the context of this invention, prevention of seizure refers to a temporary forestalling of the onset of seizure, either with or without the benefit of a warning aura.

~~[0121]~~[0114] **Midazolam** (8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo(1,5-a)benzodiazepine).



~~[0122]~~[0115] Midazolam is a tricyclic benzodiazepine having anxiolytic, amnesic, hypnotic, anticonvulsant, skeletal muscle relaxant and sedative properties. Midazolam is considered soluble in water at a pH lower than about 4, but is relatively insoluble in most aqueous solutions at neutral pH (e.g. about 6 to 8). Thus it is desirable in some embodiments for aqueous nasal preparations of midazolam to have a pH above about 5.5, preferably above about 6.0, or above about 6.5. In some preferred embodiments, the pH is between about 6 and 9, between about 6 and 8. It is considered that preparations of midazolam are particularly suitable for nasal administration as the lipid-soluble (at approximately neutral pH) midazolam is rapidly absorbed across nasal mucosa, leading to efficient uptake of midazolam. It is further considered that midazolam may be formulated in a non-aqueous delivery vehicle, such as is known in the aerosol administration art, such as hydrofluorocarbon propellants, hydrocarbon propellants, etc.

~~[0123]~~[0116] The dosage of midazolam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.1 to about 20, preferably about 0.2 to about 10 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Midazolam may be manufactured using the process disclosed in one of United States patents 4,280,957 or 5,831,089~~, each of which is incorporated herein by reference in its entirety~~.

~~[0124]~~[0117] In some embodiments, midazolam is used alone or in combination with other drugs to provide an anxiolytic effect, an anticonvulsant effect, a sedative effect, a skeletal muscle relaxant effect, an amnesic effect or combinations of the foregoing effects.

~~[0125]~~[0118] In some embodiments, midazolam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure.

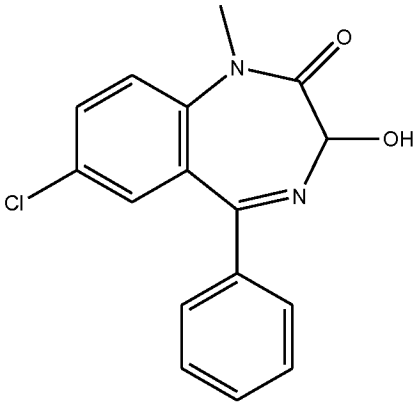
(markup)

Midazolam may be administered by the patient or other person (such as a healthcare professional) while the patient is in a non-seizing state to protect against seizure. Even where protection against seizure is not absolute, administration of midazolam may reduce or ameliorate the intensity of seizure and/or reduce or ameliorate the frequency of seizure. In some embodiments, administration of midazolam may prevent occurrence of seizure. In some embodiments, especially where the patient is prone to experiencing serial seizures or status epilepticus, administration of midazolam may aid in interrupting the seizure cycle and may thus prevent the re-occurrence of seizure. In addition to the benzodiazepines (such as diazepam), other anti-convulsant drugs may be combined with midazolam to provide a synergistic anticonvulsant effect.

[0126][0119] Midazolam may also be administered by another person (*e.g.* an acquaintance or associate, a family member or a health care professional) to the patient while the patient is in a state of seizure. Thus, one of the advantages of the formulations for use according to the present invention is the ability to administer them in an acute therapeutic environment to treat the seizure victim, for example, nasally. Among the beneficial therapeutic effects that may be imparted by acute dosing of benzodiazepine anticonvulsants, such as nasal dosing, are: reduction in the severity of the seizure (*e.g.* general relaxation of the muscles, reduction in seizure-induced anxiety experienced by the patient and a general impartation of a feeling of well-being to the patient), reduction in the duration of the seizure, reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between the current seizure and the next seizure. Thus, the midazolam formulations of the invention, and in particular nasal formulations, provide fast onset of therapeutic benefit – in some instances less than about 30 minutes, less than about 15 minutes, less than about 10 minutes, and in some cases less than about 5 minutes. The midazolam formulations of the invention, and in particular nasal formulations, also provide convenient administration of a therapeutically beneficial drug to a patient that does not require intravenous drug administration or rectal drug administration.

[0127][0120] Often seizures, particularly severe tonic or tonic-clonic seizures, will be presaged by one or more aura events that will be familiar to the patient or those familiar with the patient. These auras are practically *sui generis* for each patient, but may be classified as audible, visual, olfactory or tactile sensations that usually, or typically, precedes a patient's experiencing a seizure. In some embodiments of the invention, the method includes prompt administration of a preparation of a benzodiazepine drug according to the invention during the aura. In some embodiments, such intra-aural administration of benzodiazepine drug, for example by nasal administration, will prevent or at least ameliorate the effects (intensity, duration or both) of the impending seizure. Thus, in the context of this invention, prevention of seizure refers to a temporary forestalling of the onset of seizure, either with or without the benefit of a warning aura.

[0128][0121] **Temazepam** (7-chloro-1-methyl-5-phenyl-3-hydroxy-1,3-dihydro-2H-1,4-benzodiazepin-2-one)



~~[0129]~~[0122] Temazepam is a benzodiazepine drug having sedative, tranquilizing, anticonvulsant, amnesic and muscle relaxing properties. It is classified as an anxiolytic. Temazepam has also been shown to be useful in the treatment of nausea. The dosage of temazepam varies by indication, however it is expected that a therapeutic dose will be in the range of about 1 to about 50, preferably about 5 to about 30 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Temazepam may be manufactured using the process disclosed in United States patent 3,340,253 or 3,374,225~~, each of which is incorporated herein by reference in its entirety~~.

~~[0130]~~[0123] In some embodiments, temazepam is used alone or in combination with other drugs to provide an anxiolytic effect, an anticonvulsant effect, a sedative effect, a skeletal muscle relaxant effect, an amnesic effect or combinations of the foregoing effects.

~~[0131]~~[0124] In some embodiments, temazepam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Temazepam may be administered by the patient or other person (such as a healthcare professional) while the patient is in a non-seizing state to protect against seizure. Even where protection against seizure is not absolute, administration of temazepam may reduce or ameliorate the intensity of seizure and/or reduce or ameliorate the frequency of seizure. In some embodiments, administration of temazepam may prevent occurrence of seizure. In some embodiments, especially where the patient is prone to experiencing serial seizures or status epilepticus, administration of temazepam may aid in interrupting the seizure cycle and may thus prevent the re-occurrence of seizure. In addition to the benzodiazepines (such as diazepam), other anti-convulsant drugs may be combined with temazepam to provide a synergistic anticonvulsant effect.

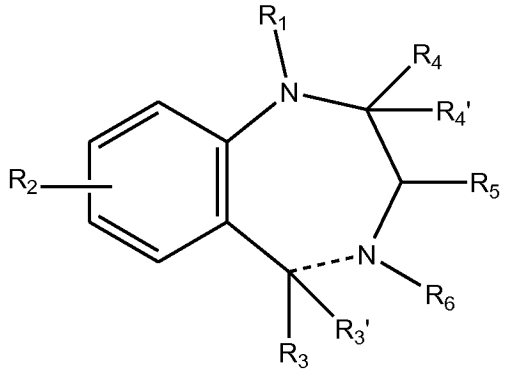
~~[0132]~~[0125] Temazepam may also be administered by another person (*e.g.* an acquaintance or associate, a family member or a health care professional) to the patient while the patient is in a state of seizure. Thus, one of the advantages of the formulations for use according to the present invention is the ability to administer them in an acute therapeutic environment to treat the seizure victim, for example, nasally. Among the beneficial therapeutic effects that may be imparted by acute dosing of benzodiazepine anticonvulsants, such as nasal dosing, are: reduction in the severity of the seizure (*e.g.* general relaxation of the muscles, reduction in seizure-induced anxiety experienced by the patient and a general impartation of a feeling of well-being to the

patient), reduction in the duration of the seizure, reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between the current seizure and the next seizure. Thus, the temazepam formulations of the invention, and in particular nasal formulations, provide fast onset of therapeutic benefit – in some instances less than about 30 minutes, less than about 15 minutes, less than about 10 minutes, and in some cases less than about 5 minutes. The temazepam formulations of the invention, and in particular nasal formulations, also provide convenient administration of a therapeutically beneficial drug to a patient that does not require intravenous drug administration or rectal drug administration.

~~[0133]~~[0126] Often seizures, particularly severe tonic or tonic-clonic seizures, will be presaged by one or more aura events that will be familiar to the patient or those familiar with the patient. These auras are practically *sui generis* for each patient, but may be classified as audible, visual, olfactory or tactile sensations that usually, or typically, precedes a patient's experiencing a seizure. In some embodiments of the invention, the method includes prompt administration of a preparation of a benzodiazepine drug according to the invention during the aura. In some embodiments, such intra-aural administration of benzodiazepine drug, for example by nasal administration, will prevent or at least ameliorate the effects (intensity, duration or both) of the impending seizure. Thus, in the context of this invention, prevention of seizure refers to a temporary forestalling of the onset of seizure, either with or without the benefit of a warning aura.

Pharmaceutically Acceptable Salts

~~[0134]~~[0127] Benzodiazepines have the generally basic structure of formula I:



Formula I

wherein R_1-R_5 are substituents. In particular embodiments, R_1 is an optionally substituted alkyl or forms a ring with R_4, R_2 is a halogen (e.g. Cl, Br), R_3 is optionally substituted aryl (e.g. 2-Chloro or 2-Fluorophenyl), R_5 is H or OH, R_4 and R_4' together form a carbonyl (C=O) with the carbon to which they are attached or R_4 and R_1 form an optionally substituted heterocyclic ring with the diazepam ring atoms to which they are respectively attached; R_3' and R_6 together form a double bond or may be combined to form an optionally substituted heterocyclic ring along with the diazepam ring atoms to which they are respectively attached. Such basic

compounds may form acid addition salts with pharmaceutically acceptable acids, such as pharmaceutically acceptable mineral acids and pharmaceutically acceptable organic acids.

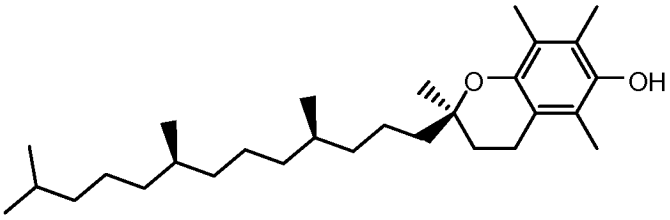
~~[0135]~~[0128] Pharmaceutically acceptable mineral acids include HCl, H_2SO_4, H_2SO_3, H_3PO_4, H_3PO_3, and others that will be recognized by those of skill in the art. Pharmaceutically acceptable organic acids include acetic acid, benzoic acid, tartaric acid, citric acid, oxalic acid, maleic acid, malonic acid, etc. Thus, in some embodiments, the pharmaceutically acceptable acid may be selected from the group consisting of: 1-hydroxy-2-naphthoic acid, 2,2-dichloroacetic acid, 2-hydroxyethanesulfonic acid, 2-oxoglutaric acid, 4-acetamidobenzoic acid, 4-aminosalicylic acid, acetic acid, adipic acidascorbic acid (L), aspartic acid (L), benzenesulfonic acid, benzoic acid, camphoric acid (+), camphor-10-sulfonic acid (+), capric acid (decanoic acid), caproic acid (hexanoic acid), caprylic acid (octanoic acid), carbonic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, formic acidfumaric acid, galactaric acid, gentisic acid, glucoheptonic acid (D), gluconic acid (D), glucuronic acid (D), glutamic acid, glutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, hydrobromic acid, hydrochloric acid, isobutyric acid, lactic acid (DL), lactobionic acid, lauric acid, maleic acid, malic acid (- L), malonic acid, mandelic acid (DL), methanesulfonic acid, benzenesulfonic acid (besylic acid), naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, nicotinic acid, nitric acid, oleic acid, oxalic acid, palmitic acid, pamoic acid, phosphoric acid, proprionic acid, pyroglutamic acid (- L), salicylic acid, sebacic acid, stearic acid, succinic acid, sulfuric acid, tartaric acid (+ L), thiocyanic acid, toluenesulfonic acid (p) and undecylenic acid. Other pharmaceutically acceptable acids may be pharmaceutically acceptable acidic (anionic) polymers or pharmaceutically acceptable amphoteric polymers. One skilled in the art will recognize that other basic active pharmaceutical ingredients may be combined with the foregoing acids to produce acid addition salts. Likewise the person skilled in the art will recognize that in some embodiments it may be advantageous that some or all of the added acid be an active pharmaceutical ingredient in its own right.

~~[0136]~~[0129] In some embodiments, the invention provides nasal compositions comprising one or more acidic pharmaceutically active ingredients. It is considered well within the ordinary skill in the art to determine which of the compounds set for the above are acidic. Such compounds may be prepared as base addition salts, e.g. by the addition of one or more mineral bases (e.g. NaOH, KOH, $NaHCO_3$, Na_2CO_3, NH_3) or organic bases. It is considered within the skill in the art to choose a pharmaceutically acceptable base.

~~[0137]~~[0130] Known benzodiazepine compounds have anxiolytic, anticonvulsant, sedative and/or skeletal muscle relaxant effect. The term “anticonvulsant” includes treatment of seizures, protection against seizure, reduction or amelioration of the intensity of seizure, reduction or amelioration of the frequency of seizure, and/or prevention of the occurrence or re-occurrence of seizure. In this regard, treatment of seizure includes cessation of an ongoing seizure, reduction in the severity of an ongoing seizure, reduction in the duration of an ongoing seizure. Protection against seizure includes forestalling an oncoming seizure.

Carrier System

~~[0138]~~[0131] Vitamin E is a class of fat soluble methylated phenols. There are at least eight naturally-occurring compounds that comprise this class: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β- tocotrienol, γ- tocotrienol, and δ- tocotrienol, all of which may be used in the compositions and methods of the present invention. There are multiple isomers of each of these compounds, all of which may be used in the compositions and methods of the present invention. There are also multiple esters of each of these compounds, including tocophersolan, all of which may be used in the compositions and methods of the present invention. As used herein, Vitamin E refers to any of the natural or synthetic tocopherols, tocotrienols, any isomers thereof, any esters thereof, any analogs or derivatives thereof, or any combinations thereof.



α-tocopherol

~~[0139]~~[0132] The compounds that comprise Vitamin E are antioxidants. There is also evidence that they can prevent, delay the onset of, or ameliorate the symptoms of heart disease, cancer, cataracts, macular degeneration, glaucoma, Alzheimer's, and Parkinson's disease.

~~[0140]~~[0133] The inventors have found that Vitamin E can provide an effective carrier for benzodiazepine drugs. In some embodiments, benzodiazepines are soluble, or partially soluble, in Vitamin E. In some embodiments, Vitamin E may be present as microparticles, nanoparticles, or any combination thereof. Furthermore, use of Vitamin E can have the added benefit of either avoiding irritation of sensitive mucosal membranes and/or soothing irritated mucosal membranes.

~~[0141]~~[0134] Vitamin E is generally classified as hydrophobic, and when used as a carrier may be limited to formulations as an emulsion. However, emulsions can have several drawbacks. For instance, they may be difficult to create and can be highly unstable. Additionally, they can leave an oily film on the surface of the skin. Thus, to avoid the drawbacks of emulsions, some embodiments of the present invention comprise solutions of one or more benzodiazepine drugs in Vitamin E and one or more lower alkyl alcohols or one or more lower alkyl glycols, or any combinations thereof.

~~[0142]~~[0135] Lower alkyl alcohols are those with six or fewer carbon atoms. Thus, any of ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, or any combinations thereof can be used.

~~[0143]~~[0136] Lower alkyl glycols are those with six or fewer carbon atoms. Thus, any of ethylene glycol, propylene glycol, butylene glycol, pentylene glycol, any isomers thereof, or any combinations thereof can be used.

Additional Excipients

~~[0144]~~[0137] In some embodiments, a composition comprises at least one penetration enhancer in addition to a benzodiazepine drug, a natural or synthetic tocopherol or tocotrienol, and an alcohol or glycol. In some embodiments, the penetration enhancer is at least one alkyl glycoside. In some embodiments, the alkyl glycoside refers to any sugar joined to any hydrophobic alkyl, as described in United States patent number 5,661,130~~, which is incorporated herein by reference in its entirety~~. The hydrophobic alkyl can be any suitable length, for example about 9 to about 24 carbons in length, especially about 10 to about 14 carbons in length. The hydrophobic alkyl can be branched and/or partially or wholly unsaturated. The alkyl may be joined to the saccharide core for example through a carbonyl group, whereby an ester group may be formed. A suitable alkyl glycoside will have the characteristics of being nontoxic, nonionic, and capable of increasing the absorption of a benzodiazepine drug when it is administered intranasally as described herein. Exemplary saccharides that may be covalently joined to an alkyl according to the present invention include glucose, maltose, maltotriose, maltotetrose, sucrose and trehalose. Exemplary alkyl glycosides that may be employed include octyl-, nonyl-, decyl-, undecyl-, dodecyl, tridecyl, tetradecyl, pentadecyl, octadecyl α- or β-D-maltoside, -glucoside or sucroside. In some embodiments, the preferred glycosides include maltose, sucrose or glucose linked by glycosidic linkage to an alkyl chain of 9, 10, 12, 14, 16, 18 or 20 carbon atoms. Specific excipients that may be employed in a nasal composition according to the invention include alkylsaccharide is dodecyl maltoside, tetradecyl maltoside, sucrose dodecanoate, sucrose monostearate, sucrose distearate, and/or combinations of two or more thereof. Alkyl glycosides that are particularly considered useful in embodiments of the invention include those marketed under the name Intravail® by Aegis Therapeutics, LLC, San Diego, CA. Other alkyl glycosides may be selected from those having a hydrophile-lipophile balance (HLB) number of from about 10-20, especially about 11-15. The HLB number may be determined as set forth in the publication US2009/0047347, published on 19 February 2009, the entirety of which, and especially paragraphs [0075]-[0079]~~, is incorporated herein by reference~~. Where present, the amount of alkyl glycoside in the composition is sufficient to enhance the absorption of a benzodiazepine drug administered by the intranasal route. In some embodiments, the amount of alkyl glycoside in the composition is selected so as to enhance absorption of the benzodiazepine drug, while at the same time not significantly irritating the nasal mucosa. In some embodiments, the amount of alkyl glycoside in the composition is in a range of about 0.01% (w/v) to about 1% (w/v). In some embodiments, the amount of alkyl glycoside in the composition is in a range of about 0.05% (w/v) to about 0.5% (w/v), or about 0.125% (w/v) to about 0.5% (w/v).

~~[0145]~~[0138] The term "penetration enhancer", means any material which acts to increase absorption across the mucosa and/or increases bioavailability. In some embodiments, such materials include mucolytic agents, degradative enzyme inhibitors and compounds which increase permeability of the mucosal cell membranes. Whether a given compound is an "enhancer" can be determined by comparing two formulations comprising a non-associated, small polar molecule as the drug, with or without the enhancer, in an in vivo or good model test and determining whether the uptake of the drug is enhanced to a clinically significant degree. The enhancer should not produce any problems in terms of chronic toxicity because in vivo the enhancer should be

non-irritant and/or rapidly metabolized to a normal cell constituent that does not have any significant irritant effect.

~~[0146]~~[0139] In some embodiments, preferred enhancing materials lysophospholipids, for example lysophosphatidylcholine obtainable from egg or soy lecithin. Other lysophosphatidylcholines that have different acyl groups as well as lyso compounds produced from phosphatidylethanolamines and phosphatidic acid which have similar membrane modifying properties may be used. Acyl carnitines (e.g. palmitoyl-dl-carnitine-chloride) is an alternative. In some embodiments, a suitable concentration is from 0.02 to 20% (w/v).

~~[0147]~~[0140] In some embodiments, enhancing agents that are appropriate include chelating agents (EGTA, EDTA, alginates), surface active agents (especially non-ionic materials), acyl glycerols, fatty acids and salts, tyloxapol and biological detergents listed in the SIGMA Catalog, 1988, page 316-321 ~~(which is incorporated herein by reference)~~. Also agents that modify the membrane fluidity and permeability are appropriate such as enamines (e.g. phenylalanine enamine of ethylacetoacetate), malonates (e.g. diethyleneoxymethylene malonate), salicylates, bile salts and analogues and fusidates. Suitable concentrations are up to 20% (w/v).

~~[0148]~~[0141] Thus, in some embodiments, the invention provides a pharmaceutical composition for nasal administration comprising: a benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); one or more alkyl glycosides; and one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w), in a pharmaceutically-acceptable formulation for administration to one or more nasal mucosal membranes of a patient. In some embodiments, the alkyl glycoside is an Intravail® brand alkyl glycoside. In some embodiments, the alkyl glycoside is dodecyl maltoside, tetradecyl maltoside, sucrose dodecanoate, sucrose monostearate, sucrose distearate, and/or a combination of two or more thereof. In some embodiments, the alkyl glycoside is dodecyl maltoside. In some embodiments, the alkyl glycoside is tetradecyl maltoside. In some embodiments, the alkyl glycoside is sucrose dodecanoate. In some embodiments, the alkyl glycoside is sucrose monostearate. In some embodiments, the alkyl glycoside is sucrose distearate. In some embodiments, the alkyl glycoside is a combination of two or more of dodecyl maltoside, tetradecyl maltoside, sucrose dodecanoate, sucrose monostearate, or sucrose distearate.

~~[0149]~~[0142] Thus, in some embodiments, the invention provides a pharmaceutical composition for nasal administration comprising: a benzodiazepine drug, which benzodiazepine drug comprises microparticles, nanoparticles or both, one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); one or more alkyl glycosides; and one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w), in a pharmaceutically-acceptable formulation for administration to one or more nasal mucosal membranes of a patient. In some embodiments, the alkyl glycoside is an Intravail® brand alkyl glycoside. In some embodiments, the alkyl glycoside is dodecyl maltoside, tetradecyl maltoside, sucrose dodecanoate, sucrose monostearate, sucrose distearate, and/or a combination of two or more thereof. In some embodiments, the alkyl glycoside is dodecyl maltoside. In some embodiments, the alkyl glycoside is tetradecyl maltoside. In some embodiments, the alkyl glycoside is sucrose dodecanoate. In some embodiments, the alkyl glycoside is

sucrose monostearate. In some embodiments, the alkyl glycoside is sucrose distearate. In some embodiments, the alkyl glycoside is a combination of two or more of dodecyl maltoside, tetradecyl maltoside, sucrose dodecanoate, sucrose monostearate, or sucrose distearate.

Mucosal Membrane Preparations

~~[0150]~~[0143] Mucosal membrane preparations are generally administered in metered sprays having volumes of less than 250 μL, preferably less than 150 μL, and ideally from 25 to 100 μL. Although not prohibited in this invention, administration of volumes larger than about 300 μL per dose usually exceeds the absorption capacity of the membranes. This results in a large portion of the pharmaceutically-active ingredient being lost.

~~[0151]~~[0144] The dosage volume of preparations, in particular nasal preparations, preferably ranges from 25 to 100 μL. Volumes in excess of the aforementioned ranges may bypass the sinuses and flow down the back of the throat where the excess is swallowed.

Alprazolam

~~[0152]~~[0145] The dosage of alprazolam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.5 to about 4, preferably about 1 to about 2 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Alprazolam may be manufactured using the process disclosed in United States patent 3,987,052~~, which is incorporated herein by reference in its entirety~~.

~~[0153]~~[0146] As a nasal formulation, alprazolam may be administered in 25 to 250 μL metered sprays. In some preferred embodiments, alprazolam is administered in 50 to 150 μL, especially about 100 μL, metered sprays

Diazepam

~~[0154]~~[0147] The dosage of diazepam may vary by indication, however it is expected that a therapeutic dose will be in the range of about 1 to about 20, preferably about 2 to about 10 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Diazepam may be manufactured using the process disclosed in one of United States patents 3,371,085, 3,109,843, 3,136,815 or 3,102,116~~, each of which is incorporated herein by reference in its entirety~~.

~~[0155]~~[0148] As a nasal formulation, diazepam may be administered in 25 to 250 μL metered sprays. In some preferred embodiments, diazepam is administered in 50 to 150 μL, especially about 100 μL, metered sprays.

Flurazepam

~~[0156]~~[0149] The dosage of flurazepam varies by indication, however it is expected that a therapeutic dose will be in the range of about 5 to 40, preferably about 20 to about 35 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Flurazepam may be manufactured using the process disclosed in United States patent 3,567,710 or 3,299,053~~, each of which is incorporated herein by reference in its entirety~~.

(markup)

~~[0157]~~[0150] As a nasal formulation, flurazepam may be administered in 25 to 250 µL metered sprays. In some preferred embodiments, flurazepam is administered in 50 to 150 µL, especially about 100 µL, metered sprays.

Lorazepam

~~[0158]~~[0151] The dosage of Lorazepam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.1 to about 10, preferably about 0.2 to about 1 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Lorazepam may be manufactured using the process disclosed in United States patent 3,296,249~~, which is incorporated herein by reference in its entirety~~.

~~[0159]~~[0152] As a nasal formulation, lorazepam may be administered in 25 to 250 µL metered sprays. In some preferred embodiments, lorazepam is administered in 50 to 150 µL, especially about 100 µL, metered sprays.

Medazepam

~~[0160]~~[0153] The dosage of medazepam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.1 to about 10, preferably about 0.2 to about 1 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Medazepam may be manufactured using the process disclosed in United States patent 3,243,427~~, which is incorporated herein by reference in its entirety~~.

~~[0161]~~[0154] As a nasal formulation, medazepam may be administered in 25 to 250 µL metered sprays. In some preferred embodiments, medazepam is administered in 50 to 150 µL, especially about 100 µL, metered sprays.

Mexazolam

~~[0162]~~[0155] The dosage of mexazolam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.1 to about 10, preferably about 0.2 to about 1 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Mexazolam may be manufactured using the process disclosed in United States patent 3,722,371~~, which is incorporated herein by reference in its entirety~~.

~~[0163]~~[0156] As a nasal formulation, mexazolam may be administered in 25 to 250 µL metered sprays. In some preferred embodiments, mexazolam is administered in 50 to 150 µL, especially about 100 µL, metered sprays.

Midazolam

~~[0164]~~[0157] The dosage of midazolam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.1 to about 20, preferably about 0.2 to about 10 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Midazolam may be manufactured using the process disclosed in one of United States patents 4,280,957 or 5,831,089~~, each of which is incorporated herein by reference in its entirety~~.

~~[0165]~~[0158] As a nasal formulation, midazolam may be administered in 25 to 250 µL metered sprays. In some preferred embodiments, midazolam is administered in 50 to 150 µL, especially about 100 µL, metered sprays.

Temazepam

~~[0166]~~[0159] The dosage of temazepam varies by indication, however it is expected that a therapeutic dose will be in the range of about 1 to about 50, preferably about 5 to about 30 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Temazepam may be manufactured using the process disclosed in United States patent 3,340,253 or 3,374,225~~, each of which is incorporated herein by reference in its entirety~~.

~~[0167]~~[0160] As a nasal formulation, temazepam may be administered in 25 to 250 µL metered sprays. In some preferred embodiments, temazepam is administered in 50 to 150 µL, especially about 100 µL, metered sprays.

Formulation

~~[0168]~~[0161] Some embodiments comprise administering to one or more mucosal membranes of a patient a therapeutically effective amount of one or more benzodiazepine drugs, or pharmaceutically-acceptable salts thereof. Some embodiments of the composition disclose a composition comprising one or more benzodiazepine drugs or pharmaceutically-acceptable salts thereof in a concentration up to about 600 mg/mL. Other compositions disclose a composition comprising one or more benzodiazepine drugs or pharmaceutically-acceptable salts thereof in a concentration of about 10 mg/mL up to about 250 mg/mL. Further, some embodiments disclose a composition comprising one or more benzodiazepine drugs or pharmaceutically-acceptable salts thereof in a concentration of about 20 mg/mL up to about 50 mg/mL.

~~[0169]~~[0162] Some embodiments disclose a carrier system that is about 50% to about 90% (w/w) Vitamin E and about 10% to about 50% (w/w) lower alcohol or lower alkyl glycol, or any combinations thereof. Some embodiments disclose a carrier system that is about 65% to about 75% (w/w) Vitamin E and about 25% to about 35% (w/w) lower alkyl alcohol or lower alkyl glycol, or any combinations thereof. Further, some embodiments disclose a carrier system that is about 70% (w/w) Vitamin E and about 30% (w/w) lower alkyl alcohol or lower alkyl glycol, or any combinations thereof.

~~[0170]~~[0163] Some embodiments of the invention provide a method of administering the benzodiazepine drug composition to a patient. The preferred embodiment comprises use of diazepam. Some embodiments of the method disclose a dosage level of diazepam of about 1.0 mg to about 20.0 mg until achievement of the desired result. Other dosage levels disclose a dosage level of about 2.0 mg to about 15.0 mg until the desired result is achieved. Some embodiments disclose a dosage level of about 5.0 mg to about 10.0 mg until the desired result is achieved.

~~[0171]~~[0164] In some embodiments of the method, the dosage volume ranges from about 10 µL to about 200 µL. In some embodiments, the dosage volume ranges from about 20 µL to about 180 µL. Further, some

embodiments disclose a dosage volume of about 50 µL to about 140 µL. In some embodiments, the dosage volume is 50 µL, 75 µL or 100 µL per nostril.

Formulation Process

~~[0172]~~[0165] In some embodiments, the composition for nasal administration is substantially free of benzodiazepine microparticles, nanoparticles or combinations thereof. In some embodiments, the composition is made by slowly warming or heating the Vitamin E until it is liquefied. Next, the one or more benzodiazepine drugs are added. The mixture is stirred and heated until the one or more benzodiazepine drugs dissolve or are substantially dissolved. Next, the one or more alcohols or glycols, or any combinations thereof, are added to the composition. This composition is stirred until a less viscous composition is achieved.

~~[0173]~~[0166] The formulation process may be adjusted to take into consideration variations in the formulation. For example, as depicted in Figure 4, formulations comprising both benzyl alcohol and ethanol may be formulated by first combining Vitamin E, benzyl alcohol and ethanol (*e.g.*, dehydrated alcohol, USP), mixing until the ingredients are homogenous, heating the mixture to about 45°C (±2°C), adding alkyl glocoside and mixing until the alkyl glycoside is dissolved and the solution is homogenous, adding benzodiazepine (*e.g,* diazepam) while maintaining the mixture at about 45 °C, cooling the solution to about 25°C (±2°C) and adding ethanol (Q.S.) to achieve the final target weight of solution, mixing well to assure homogeneity. Solutions manufactured according to this process may be formulated in different concentrations of diazepam. For example, some embodiments of the invention include diazepam formulations summarized in the following table. While diazepam is used as an illustration in Figure 4 and the following table, any benzodiazepines may also be used, such as alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, any pharmaceutically-acceptable salts thereof, and any combinations thereof.

~~[0174]~~[0167] NRL-1 Quantitative Composition. ~~In some embodiments, t~~The formulations are for nasal administration.

Component	Solution Concentration		
	50mg/mL	**75 mg/mL**	**100 mg/mL**
Vitamin E	56.47 mg	56.47 mg	56.47 mg
Benzyl alcohol	10.50 mg	10.50 mg	10.50 mg
Diazepam	5.00 mg	7.50 mg	10.00 mg
Intravail A3®	0.25 mg	0.25 mg	0.25 mg
Dehydrated ethanol	q.s. to 100µL	q.s. to 100µL	q.s. to 100µL

~~[0175]~~[0168] In some embodiments, the aforementioned formulations are sterile solutions with a bacteria count of 10 below the allowable level on a per mL basis. Additionally, pathogens are preferably absent. In some embodiments, the solutions are self-preserving, self-sterile or both.

~~[0176]~~[0169] In some embodiments, the benzodiazepine drug is formulated as a microparticulate and/or nanoparticulate suspension of the benzodiazepine. Preparation of microparticulate and nanoparticulate benzodiazepine may be accomplished by methods such as milling, etc. Such methods are known to those skilled in the art.

~~[0177]~~[0170] Figure 5 depicts one embodiment of a process of manufacturing a suspension of benzodiazepine according to the instant invention. First, the benzodiazepine (*e.g.*, diazepam) is sieved to produce a micronized benzodiazepine (*e.g.*, diazepam). The micronized benzodiazepine (*e.g.*, diazepam) is then split into two intermediates products - Diazepam A (high pressure) is a small particle size (mean particle size < 2000 nm) and Diazepam B (low pressure) is a large particle size (mean particle diameter > 2000 nm). After in-process testing, the two intermediate products are combined with one or more excipients in correct proportions to produce a bimodal particle suspension having a pre-selected mean particle diameter, which in some embodiments is greater than 2000 nm. In some embodiments, the excipients are prepared according to the second column in Figure 5, *e.g.* by first combining propylene glycol, water and vitamin E polyethylene glycol succinate to form a mixture and heating the mixture until the ingredients are dissolved, then adding methylparaben, propyl paraben and Intravail™ (alkyl glycoside) to the mixture and mixing until the newly added ingredients are dissolved, and finally cooling the mixture, *e.g.* to 25°C ± 2°C. The excipients can then be combined with Micronized Diazepam A and Micronized Diazepam B and mixed vigorously to disperse the micronized Diazepam to form the suspension. Next, povidone is added to the mixture, which is mixed until the povidone is fully dissolved. Finally, the suspension is brought to its final target weight with purified water and mixed well to achieve homogeneity. The final product can then be filled into suitable containers. In some embodiments, 3 mL may be filled into 4 mL amber glass vials with PTFE lined phenolic closures, though other containers are of course possible and contemplated within the scope of the invention. As diazepam is depicted in Figure 5 as an exemplary benzodiazepine, any benzodiazepines, such as alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, any pharmaceutically-acceptable salts thereof, and any combinations thereof may also be employed.

~~[0178]~~[0171] ~~In some embodiments, the aforementioned formulations are sterile suspensions with a bacteria count of 10 below the allowable level on a per mL basis. Additionally, pathogens are preferably absent. In some embodiments, the suspensions are self-preserving, self-sterile or both.~~

~~[0179]~~[0172] In some embodiments, the benzodiazepine drug is formulated as a solution. It is considered an aspect of the invention that employment of microparticulate and/or nanoparticulate benzodiazepine drug during the process of preparing the formulation, can improve the overall solubility of the benzodiazepine drug in the solvent system.

(markup)

Additional Active and Inactive Ingredients

~~[0180]~~[0173] Additionally, some embodiments of the compositions and methods of using the compositions comprise an additional ingredient in the composition selected from active ingredients. By way of non-limiting example, such active ingredients include insulin, calcitonins (for example porcine, human, salmon, chicken, or eel) and synthetic modifications thereof, enkephalins, LHRH and analogues (Nafarelin, Buserelin, Zolidex), GHRH (growth hormone releasing hormone), nifedipin, THF (thymic humoral factor), CGRP (calcitonin gene related peptide), atrial natriuretic peptide, antibiotics, metoclopramide, ergotamine, Pizotizin, nasal vaccines (particularly HIV vaccines, measles, rhinovirus Type 13 and respiratory syncitial virus), pentamidine, CCK (Cholecystikinine), DDVAP, Interferons, growth hormone (solatotropir polypeptides or their derivatives (preferably with a molecular weight from 1000 to 300000), secretin, bradykinin antagonists, GRF (Growth releasing factor), THF, TRH (Thyrotropin releasing hormone), ACTH analogues, IGF (Insulin like growth factors), CGRP (Calcitorin gene related peptide) Atrial Natriuretic peptide, Vasopressin and analogues (DDAVP, Lypressin), Metoclopramide, Migraine treatment (Dihydroergotamine, Ergometrine, Ergotamine, Pizotizin), Nasal Vaccines (Particularly AIDS vaccines) FACTOR VIII, Colony Stimulating factors, G-CSF (granulocyte-colony stimulating factor), EPO (Erythropoitin) PTH (Parathyroid hormone) or pharmaceutically acceptable salts or combinations thereof.

~~[0181]~~[0174] Additionally, some embodiments of the compositions and methods of using the compositions comprise an additional ingredient in the composition selected from other anticonvulsants. By way of non-limiting example, such active ingredients include: paraldehyde; aromatic allylic alcohols (such as stiripentol); barbiturates (e.g. phenobarbitol, primidone, methylphenobarbital, metharbital and barbexaclone); bromides (such as potassium bromide); carbamates (such as felbamate); carboxamides (such as carbamazepine and oxcarbazepine); fatty acids (such as valproic acid, sodium valproate, and divalproex sodium, vigabatrin, progabide, tiagabine); fructose, topiramate, Gaba analogs (e.g. gabapentin and pregabalin); hydantoins (e.g. ethotoin, phenytoin, mephenytoin and fosphenytoin); oxazolidinediones (such as paramethadione, trimethadione, ethadione); propionates (e.g. beclamide), pyrimidinediones (e.g. primidone); pyrrolidines (e.g. brivaracetam, levetiracetam and seletracetam); succinimides (e.g. ethosuximide, phensuximide and mesuximide); sulfonamides (e.g. acetazolamide, sulthiame, methazolamide and zonisamide); triazines (such as lamotrigine); ureas (such as pheneturide, phenacemide); valproylamides (such as valpromide and valnoctamide); as well as other anticonvulsants or pharmaceutically acceptable salts or combinations thereof.

~~[0182]~~[0175] Additionally, some embodiments of the compositions and methods of using the compositions comprise an additional ingredient in the composition selected from other anticonvulsants. By way of non-limiting example, such active ingredients include: antibiotics and antimicrobial agents such as tetracyline hydrochloride, leucomycin, penicillin, penicillin derivatives, erythromycin, gentamicin, sulphathiazole and nitrofurazone; local anaesthetics such as benzocaine; vasoconstrictors such as phenylephrine hydrochloride, tetrahydrozoline hydrochloride, naphazoline nitrate, oxymetazoline hydrochloride and tramazoline hydrochloride; cardiotonics such as digitalis and digoxin; vasodilators such as nitroglycerine and papaverine hydrochloride; antiseptics such as chlorhexidine hydrochloride, hexylresorcinol, dequaliniumchloride and

ethacridine; enzymes such as lysozyme chloride, dextranase; bone metabolism controlling agents such as vitamin D, active vitamin D and vitamin C; sex hormones; hypotensives; sedatives; anti-tumor agents; steroidal anti-inflammatory agents such as hydrocortisone, prednisone, fluticasone, prednisolone, triamcinolone, triamcinolone acetonide, dexamethasone, betamethasone, beclomethasone, and beclomethasone dipropionate; non-steroidal anti-inflammatory agents such as acetaminophen, aspirin, aminopyrine, phenylbutazone, medanamic acid, ibuprofen, diclofenac sodium, indomethacine, colchicine, and probenocid; enzymatic anti-inflammatory agents such as chymotrypsin and bromelain seratiopeptidase; anti-histaminic agents such as diphenhydramine hydrochloride, chloropheniramine maleate and clemastine; anti-allergic agents and antitussive-expectorant antasthmatic agents such as sodium chromoglycate, codeine phosphate, and isoproterenol hydrochloride or pharmaceutically acceptable salts or combinations thereof.

~~[0183]~~[0176] Additionally, some embodiments of the compositions and methods of using the compositions comprise an additional inactive ingredient in the composition. By way of non-limiting example, minor amounts of ingredients such as stabilizers, coloring agents, pH adjusters, buffering agents, preservatives such as agents which may prevent degradation, wetting agents, and flavoring agents may also be present. Examples of coloring agents include β-carotene, Red No. 2 and Blue No. 1. Examples of preservatives include stearic acid, ascorbyl stearate and ascorbic acid. Examples of corrigents include menthol and citrus perfume.

~~[0184]~~[0177] In some embodiments, the drug delivery system of the invention may advantageously comprise an absorption enhancer. The term "enhancer", means any material which acts to increase absorption across the mucosa and/or increases bioavailability. In some embodiments, such materials include mucolytic agents, degradative enzyme inhibitors and compounds which increase permeability of the mucosal cell membranes. Whether a given compound is an "enhancer" can be determined by comparing two formulations comprising a non-associated, small polar molecule as the drug, with or without the enhancer, in an in vivo or good model test and determining whether the uptake of the drug is enhanced to a clinically significant degree. The enhancer should not produce any problems in terms of chronic toxicity because in vivo the enhancer should be non-irritant and/or rapidly metabolized to a normal cell constituent that does not have any significant irritant effect.

~~[0185]~~[0178] In some embodiments, preferred enhancing materials lysophospholipids, for example lysophosphatidylcholine obtainable from egg or soy lecithin. Other lysophosphatidylcholines that have different acyl groups as well as lyso compounds produced from phosphatidylethanolamines and phosphatidic acid which have similar membrane modifying properties may be used. Acyl carnitines (e.g. palmitoyl-dl-carnitine-chloride) is an alternative. In some embodiments, a suitable concentration is from 0.02 to 20% (w/v).

~~[0186]~~[0179] In some embodiments, enhancing agents that are appropriate include chelating agents (EGTA, EDTA, alginates), surface active agents (especially non-ionic materials), acyl glycerols, fatty acids and salts, tyloxapol and biological detergents listed in the SIGMA Catalog, 1988, page 316-321 ~~(which is incorporated herein by reference)~~. Also agents that modify the membrane fluidity and permeability are appropriate such as enamines (e.g. phenylalanine enamine of ethylacetoacetate), malonates (e.g. diethyleneoxymethylene malonate), salicylates, bile salts and analogues and fusidates. Suitable concentrations are up to 20% (w/v).

(markup)

~~[0187]~~[0180] In some embodiments, the invention takes advantage of delivery of a drug incorporated into or onto a bioadhesive microsphere with an added pharmaceutical adjuvant applies to systems that contain active drug and mucolytic agent, peptidase inhibitors or non-drug polypeptide substrate singly or in combination. Suitably mucolytic agents are thiol-containing compounds such as N-acetylcysteine and derivatives thereof. Peptide inhibitors include actinonin, amastatin, bestatin, chloroacetyl-HOLeu-Ala-Gly-NH.sub.2, diprotin A and B, ebelactone A and B, E-64, leupeptin, pepstatin A, phisphoramidon, H-Thr-(tBu)-Phe-Pro-OH, aprotinin, kallikrein, chymostatin, benzamidine, chymotrypsin and trypsin. Suitable concentrations are from 0.01 to 10% (w/v). The person skilled in the art will readily be able to determine whether an enhancer should be included.

Administration

~~[0188]~~[0181] In some embodiments, the administration of the composition comprises administering at least a portion of the therapeutically effective amount of the composition onto at least one mucosal membrane. In some embodiments, the administration of the composition comprises spraying at least a portion of the therapeutically effective amount of the composition into at least one nostril. In some embodiments, the administration of the composition comprises spraying at least a portion of the therapeutically effective amount of the composition into each nostril. In some embodiments, the administration of the composition comprises spraying a first quantity of the composition into the first nostril, spraying a second quantity of the composition into a second nostril, and optionally after a pre-selected time delay, spraying a third quantity of the composition into the first nostril. Some embodiments further comprise, optionally after a pre-selected time delay, administering at least a fourth quantity of the composition to the second nostril.

Alprazolam

~~[0189]~~[0182] The dosage of alprazolam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.5 to about 4, preferably about 1 to about 2 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Alprazolam may be manufactured using the process disclosed in United States patent 3,987,052~~, which is incorporated herein by reference in its entirety~~.

~~[0190]~~[0183] As a nasal formulation, alprazolam may be administered in 25 to 250 µL metered sprays. In some preferred embodiments, alprazolam is administered in 50 to 150 µL, especially about 100 µL, metered sprays. In some embodiments, a first metered spray is applied to a first nostril and if necessary a second metered spray is applied to a second nostril. In some optional embodiments, a third metered spray is applied to the first nostril. In some embodiments, a fourth metered spray is applied to the second nostril. In some embodiments, additional metered sprays are applied to alternating nostrils until the full target therapeutic dose has been administered to the patient. In some embodiments, there is a time increment of from several seconds to 5 minutes, preferably about 10 seconds to about 1 minute, between applications of benzodiazepine drug to the same nostril. This allows time for the drug to cross the nasal mucosa and enter the blood stream. Multiple applications of metered sprays to each nostril, optionally separated by a time interval, allows administration of

a full therapeutic dose in increments small enough to permit full absorption of the benzodiazepine drug into the blood stream and avoid loss of drug down the back of the throat.

Diazepam

~~[0191]~~[0184] The dosage of diazepam may vary by indication, however it is expected that a therapeutic dose will be in the range of about 1 to about 20, preferably about 2 to about 10 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Diazepam may be manufactured using the process disclosed in one of United States patents 3,371,085, 3,109,843, 3,136,815 or 3,102,116~~, each of which is incorporated herein by reference in its entirety~~.

~~[0192]~~[0185] As a nasal formulation, diazepam may be administered in 25 to 250 µL metered sprays. In some preferred embodiments, diazepam is administered in 50 to 150 µL, especially about 100 µL, metered sprays. In some embodiments, a first metered spray is applied to a first nostril and if necessary a second metered spray is applied to a second nostril. In some optional embodiments, a third metered spray is applied to the first nostril. In some embodiments, a fourth metered spray is applied to the second nostril. In some embodiments, additional metered sprays are applied to alternating nostrils until the full target therapeutic dose has been administered to the patient. In some embodiments, there is a time increment of from several seconds to 5 minutes, preferably about 10 seconds to about 1 minute, between applications of benzodiazepine drug to the same nostril. This allows time for the drug to cross the nasal mucosa and enter the blood stream. Multiple applications of metered sprays to each nostril, optionally separated by a time interval, allows administration of a full therapeutic dose in increments small enough to permit full absorption of the benzodiazepine drug into the blood stream and avoid loss of drug down the back of the throat.

Flurazepam

~~[0193]~~[0186] The dosage of flurazepam varies by indication, however it is expected that a therapeutic dose will be in the range of about 5 to 40, preferably about 20 to about 35 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Flurazepam may be manufactured using the process disclosed in United States patent 3,567,710 or 3,299,053~~, each of which is incorporated herein by reference in its entirety~~.

~~[0194]~~[0187] As a nasal formulation, flurazepam may be administered in 25 to 250 µL metered sprays. In some preferred embodiments, flurazepam is administered in 50 to 150 µL, especially about 100 µL, metered sprays. In some embodiments, a first metered spray is applied to a first nostril and if necessary a second metered spray is applied to a second nostril. In some optional embodiments, a third metered spray is applied to the first nostril. In some embodiments, a fourth metered spray is applied to the second nostril. In some embodiments, additional metered sprays are applied to alternating nostrils until the full target therapeutic dose has been administered to the patient. In some embodiments, there is a time increment of from several seconds to 5 minutes, preferably about 10 seconds to about 1 minute, between applications of benzodiazepine drug to the same nostril. This allows time for the drug to cross the nasal mucosa and enter the blood stream. Multiple applications of metered sprays to each nostril, optionally separated by a time interval, allows administration of

a full therapeutic dose in increments small enough to permit full absorption of the benzodiazepine drug into the blood stream and avoid loss of drug down the back of the throat.

Lorazepam

~~[0195]~~[0188] The dosage of Lorazepam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.1 to about 10, preferably about 0.2 to about 1 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Lorazepam may be manufactured using the process disclosed in United States patent 3,296,249~~, which is incorporated herein by reference in its entirety~~.

~~[0196]~~[0189] As a nasal formulation, lorazepam may be administered in 25 to 250 µL metered sprays. In some preferred embodiments, lorazepam is administered in 50 to 150 µL, especially about 100 µL, metered sprays. In some embodiments, a first metered spray is applied to a first nostril and if necessary a second metered spray is applied to a second nostril. In some optional embodiments, a third metered spray is applied to the first nostril. In some embodiments, a fourth metered spray is applied to the second nostril. In some embodiments, additional metered sprays are applied to alternating nostrils until the full target therapeutic dose has been administered to the patient. In some embodiments, there is a time increment of from several seconds to 5 minutes, preferably about 10 seconds to about 1 minute, between applications of benzodiazepine drug to the same nostril. This allows time for the drug to cross the nasal mucosa and enter the blood stream. Multiple applications of metered sprays to each nostril, optionally separated by a time interval, allows administration of a full therapeutic dose in increments small enough to permit full absorption of the benzodiazepine drug into the blood stream and avoid loss of drug down the back of the throat.

Medazepam

~~[0197]~~[0190] The dosage of medazepam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.1 to about 10, preferably about 0.2 to about 1 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Medazepam may be manufactured using the process disclosed in United States patent 3,243,427~~, which is incorporated herein by reference in its entirety~~.

~~[0198]~~[0191] As a nasal formulation, medazepam may be administered in 25 to 250 µL metered sprays. In some preferred embodiments, medazepam is administered in 50 to 150 µL, especially about 100 µL, metered sprays. In some embodiments, a first metered spray is applied to a first nostril and if necessary a second metered spray is applied to a second nostril. In some optional embodiments, a third metered spray is applied to the first nostril. In some embodiments, a fourth metered spray is applied to the second nostril. In some embodiments, additional metered sprays are applied to alternating nostrils until the full target therapeutic dose has been administered to the patient. In some embodiments, there is a time increment of from several seconds to 5 minutes, preferably about 10 seconds to about 1 minute, between applications of benzodiazepine drug to the same nostril. This allows time for the drug to cross the nasal mucosa and enter the blood stream. Multiple applications of metered sprays to each nostril, optionally separated by a time interval, allows administration of

a full therapeutic dose in increments small enough to permit full absorption of the benzodiazepine drug into the blood stream and avoid loss of drug down the back of the throat.

Mexazolam

~~[0199]~~[0192] The dosage of mexazolam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.1 to about 10, preferably about 0.2 to about 1 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Mexazolam may be manufactured using the process disclosed in United States patent 3,722,371~~, which is incorporated herein by reference in its entirety~~.

~~[0200]~~[0193] As a nasal formulation, mexazolam may be administered in 25 to 250 µL metered sprays. In some preferred embodiments, mexazolam is administered in 50 to 150 µL, especially about 100 µL, metered sprays. In some embodiments, a first metered spray is applied to a first nostril and if necessary a second metered spray is applied to a second nostril. In some optional embodiments, a third metered spray is applied to the first nostril. In some embodiments, a fourth metered spray is applied to the second nostril. In some embodiments, additional metered sprays are applied to alternating nostrils until the full target therapeutic dose has been administered to the patient. In some embodiments, there is a time increment of from several seconds to 5 minutes, preferably about 10 seconds to about 1 minute, between applications of benzodiazepine drug to the same nostril. This allows time for the drug to cross the nasal mucosa and enter the blood stream. Multiple applications of metered sprays to each nostril, optionally separated by a time interval, allows administration of a full therapeutic dose in increments small enough to permit full absorption of the benzodiazepine drug into the blood stream and avoid loss of drug down the back of the throat.

Midazolam

~~[0201]~~[0194] The dosage of midazolam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.1 to about 20, preferably about 0.2 to about 10 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Midazolam may be manufactured using the process disclosed in one of United States patents 4,280,957 or 5,831,089~~, each of which is incorporated herein by reference in its entirety~~.

~~[0202]~~[0195] As a nasal formulation, midazolam may be administered in 25 to 250 µL metered sprays. In some preferred embodiments, midazolam is administered in 50 to 150 µL, especially about 100 µL, metered sprays. In some embodiments, a first metered spray is applied to a first nostril and if necessary a second metered spray is applied to a second nostril. In some optional embodiments, a third metered spray is applied to the first nostril. In some embodiments, a fourth metered spray is applied to the second nostril. In some embodiments, additional metered sprays are applied to alternating nostrils until the full target therapeutic dose has been administered to the patient. In some embodiments, there is a time increment of from several seconds to 5 minutes, preferably about 10 seconds to about 1 minute, between applications of benzodiazepine drug to the same nostril. This allows time for the drug to cross the nasal mucosa and enter the blood stream. Multiple applications of metered sprays to each nostril, optionally separated by a time interval, allows administration of

a full therapeutic dose in increments small enough to permit full absorption of the benzodiazepine drug into the blood stream and avoid loss of drug down the back of the throat.

Temazepam

~~[0203]~~[0196] The dosage of temazepam varies by indication, however it is expected that a therapeutic dose will be in the range of about 1 to about 50, preferably about 5 to about 30 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Temazepam may be manufactured using the process disclosed in United States patent 3,340,253 or 3,374,225~~, each of which is incorporated herein by reference in its entirety~~.

~~[0204]~~[0197] As a nasal formulation, temazepam may be administered in 25 to 250 µL metered sprays. In some preferred embodiments, temazepam is administered in 50 to 150 µL, especially about 100 µL, metered sprays. In some embodiments, a first metered spray is applied to a first nostril and if necessary a second metered spray is applied to a second nostril. In some optional embodiments, a third metered spray is applied to the first nostril. In some embodiments, a fourth metered spray is applied to the second nostril. In some embodiments, additional metered sprays are applied to alternating nostrils until the full target therapeutic dose has been administered to the patient. In some embodiments, there is a time increment of from several seconds to 5 minutes, preferably about 10 seconds to about 1 minute, between applications of benzodiazepine drug to the same nostril. This allows time for the drug to cross the nasal mucosa and enter the blood stream. Multiple applications of metered sprays to each nostril, optionally separated by a time interval, allows administration of a full therapeutic dose in increments small enough to permit full absorption of the benzodiazepine drug into the blood stream and avoid loss of drug down the back of the throat.

~~[0205]~~[0198] Those skilled in the art will be aware that a systematic, therapeutically effective amount of benzodiazepine drugs for treating the aforementioned disorders will vary with age, size, weight, and general physical condition of the patient as well as the severity of the disease. Frequency of administration will likewise vary with the formulation of the composition and it can be adjusted so that any suitable number of doses per day may be used.

Examples

~~[0206]~~[0199] The invention will now be illustrated with reference to the following illustrative, non-limiting examples.

Example 1

~~[0207]~~[0200] A pharmaceutical composition comprising diazepam is prepared. It is formulated as a solution to be delivered via a nasal delivery device. The composition is used to treat or prevent seizures associated with epilepsy in adults. Treatment is administered either before or after a seizure has begun. If the patient is seizing, it is administered as 1 puff from any nasal delivery device (1 puff at 5.0 mg/puff (5.0 mg/0.1 mL and 0.1 mL/puff)) every 5 minutes until cessation of the seizure. However, it can be given as 1 puff per nostril in

each nostril (2 puffs at 2.5 mg/puff (5.0 mg/0.1 mL and 0.05 mL/puff)) every 5 minutes until cessation of the seizure. The composition according to this example is set forth in the following table.

Table 1-1 (not claimed)

5.0 mg/0.1mL	Diazepam
70.0 mg	α-tocopherol
0.1 mL	ethanol (qs ad to 0.1 mL)

Example 2

~~[0208]~~[0201] A pharmaceutical composition comprising diazepam is prepared. It is formulated as a solution to be delivered via a nasal delivery device. The composition is used to treat or prevent seizures associated with epilepsy in children. Treatment is administered either before or after a seizure has begun. If the patient is seizing, it is administered as 1 puff from any nasal delivery device (1 puff at 2.0 mg/puff (2.0 mg/0.1 mL and 0.1 mL/puff)). If the seizure fails to stop another dose may be administered after 5 minutes. However, it can be given as 1 puff per nostril in each nostril (2 puffs at 1.0 mg/puff (2.0 mg/0.1 mL and 0.05 mL/puff)). If the seizure fails to stop another dose may be administered after 5 minutes. The composition according to this example is set forth in the following table.

Table 2-1 (not claimed)

2.0 mg/0.1mL	Diazepam
70.0 mg	α-tocopherol
0.1 mL	ethanol (qs ad to 0.1 mL)

Example 3 – Formulation of Diazepam Solutions

~~[0209]~~[0202] In general, benzodiazepine solutions may be formulated by combining one or more natural or synthetic tocopherols or tocotrienols and one or more lower alcohols or glycols and mixing until a homogeneous mixture is formed, adding the benzodiazepine drug to the homogeneous mixture, heating and mixing the ingredients until the benzodiazepine is fully dissolved in the homogeneous mixture, cooling the mixture, and bringing the mixture to its final mass or volume with lower alcohol or glycol.

~~[0210]~~[0203] Two different diazepam solutions were formulated by the foregoing process. Vitamin E USP and dehydrated ethanol USP were combined in the amounts set forth in the following table and mixed to form a homogeneous mixture. Diazepam in the amounts set forth in the following table was then added to the homogeneous mixture. The ingredients were heated to 40-45°C with mixing until the diazepam was fully dissolved, thereby forming a solution. The solution was cooled to 20-25°C, whereupon the solution was brought to its final target weight with dehydrated ethanol USP and the solution was mixed thoroughly to

assure homogeneity. The solution was then sampled for in-process testing and packaged in 3 mL amber glass vials.

Table 3-1: Diazepam Solutions – 70 mg/mL (not claimed)

Component	Solution 00 (65% Vitamin E) Concentration (mg/mL)	Solution 02 (80% Vitamin E) Concentration (mg/mL)
Diazepam USP	70.0	70.0
Vitamin E USP	650.0	800.0
Dehydrated Ethanol USP	q.s. to 1 mL	q.s. to 1 mL

~~[0211]~~[0204] Additional solutions of diazepam at varying concentrations are made in a similar manner, by varying the amount of diazepam and the relative amounts of Vitamin E and ethanol. Other benzodiazepine solutions are made by substituting one or more benzodiazepines for diazepam. Other ingredients, such as alkyl glycoside, can be added at a suitable step in the process (e.g. before or concurrently with the addition of benzodiazepine).

~~**Example 4 – Formulation of Diazepam Suspensions (not claimed)**~~

~~[0212]~~[0205] ~~In general, benzodiazepine suspensions are formulated by micronizing benzodiazepine and combining the benzodiazepine with a carrier. The carrier is prepared by combining one or more lower alcohols or glycols with water, adding a natural or synthetic tocopherol or tocotrienol, heating the mixture until the tocopherol or tocotrienol is dissolved, adding one or more parabens and mixing until the parabens are dissolved and cooling the carrier. Once the benzodiazepine is added to the carrier, additional excipients, such as surfactants, can optionally be added and dissolved in the carrier. The suspension is then brought up to its final mass or volume with water.~~

~~[0213]~~[0206] ~~Two different diazepam suspensions were formulated by the foregoing general process. Two different diazepam particle sizes were prepared – A: a small particle size by prepared by high pressure micronization, and B: a large particle size prepared by low pressure micronization. The carrier was prepared by combining propylene glycol USP and purified water USP, then adding Vitamin E Polyethylene Glycols Succinate NF, then mixing and heating the combined ingredients to about 45°C. Mixing was continued until the Vitamin E Polyethylene Glycol Succinate was fully dissolved. The carrier was then cooled to 20-25°C. The micronized diazepam (A and B) was then added to the carrier with vigorous mixing until the diazepam was fully dispersed in the carrier. Polyvinylpyrrolidone Povidone USP/NF was then added to the mixture and mixed until fully dissolved. The suspension was then brought up to weight with purified water USP. The suspension was then mixed until homogeneous, sampled for in-process testing, and packaged in 3 mL amber glass bottles.~~

~~Table 4-1: Diazepam Suspension Formulations~~

~~Component~~	~~Suspension 03 (200 mg/mL Diazepam) Concentration (mg/mL)~~	~~Suspension 01 (100 mg/mL Diazepam) Concentration (mg/mL)~~
~~Diazepam USP~~	~~200.00~~	~~100.00~~
~~Vitamin E Polyethylene Glycol Succinate NF~~	~~100.0~~	~~100.0~~
~~Methylparaben NF~~	~~2.0~~	~~2.0~~
~~Propylparaben NF~~	~~0.5~~	~~0.5~~
~~Propylene Glycol USP~~	~~100.0~~	~~100.0~~
~~Povidone USP/NF~~	~~25.0~~	~~25.0~~
~~Purified Water USP/EP~~	~~q.s. to 1 mL~~	~~q.s. to 1 mL~~

~~[0214]~~[0207] ~~Additional suspensions of diazepam at varying concentrations are made in a similar manner, by varying the amount of diazepam and optionally other excipients. Other benzodiazepine suspensions are made by substituting one or more benzodiazepines for diazepam. Other ingredients, such as alkyl glycoside, can be added at a suitable step in the process. For example, an alkylglycoside may be added to the carrier during compounding of the carrier, or may be added to the suspension mixture concurrently with or after addition of the povidone.~~

Example 5 -- Stability of Diazepam Solutions ~~and Suspensions~~

~~[0215]~~[0208] Solutions 00 and 02 (Example 3) ~~and Suspensions 01 and 03 (Example 4) (not claimed)~~ were set up on stability at 25°C / 60% RH, 30°C / 65% RH and 40°C / 75% RH. One batch each of ~~four~~ the two different formulations, packaged in 3-ml vials with screw-top closures, along with corresponding actuators, were set up at three storage conditions. They are listed in Table 1 with their corresponding Particle Sciences initial sample control numbers.

Table 5-1: Summary of PSI sample control numbers

Formulation #	**25°C/60% RH**	**30°C/65% RH**	**40°C/75% RH**
Solution 00 – 70 mg/ml solution, 65% Vitamin E	083101.01	083101.02	083101.02
Solution 02 – 70 mg/ml solution, 80% vitamin E	083102.01	083102.02	083102.03
~~Suspension 01 – 100 mg/ml suspension~~	~~083103.01~~	~~083103.02~~	~~083103.03~~
~~Suspension 03 – 200 mg/ml suspension~~	~~083104.01~~	~~083104.02~~	~~083104.03~~

(markup)

~~[0216]~~[0209] ~~Samples were tested for spray content uniformity, spray volume, diazepam content, diazepam related substances, and methylparaben and propylparaben assay (suspension samples only). Unit weights were determined as per USP <755>.~~

~~[0217]~~[0210] Summaries of the average assay values and all other results are given in Tables 5-4, 5-5,~~ 5-6 and 5-7~~. The results for the initial, 1-month and 3-month time points are also shown for comparison. Individual spray content uniformity results are given in Tables 5-8, 5-9, 5-10, and 5-11,~~, 5-12, 5-13, 5-14, and 5-15~~.

~~[0218]~~[0211] In general, all of the assays and the other results are similar to the initial data, with the exceptions of diazepam related compounds A and B.

~~[0219]~~[0212] Related compound A did not meet the specification of not more than (NMT) 0.01% for some samples (see Table 2). Related compound A has increased with time and temperature.

Table 5-2: Summary of related compound A T6M results

Solution/Suspension #	25°C/60% RH	30°C/65% RH	40°C/75% RH
Solution 00	Meets specification	0.058%	0.051%
Solution 02	Meets specification	Meets specification	Meets specification
~~Suspension 01~~	~~0.038%~~	~~0.046%~~	~~0.157%~~
~~Suspension 03~~	~~0.019%~~	~~0.029%~~	~~0.081%~~

~~[0220]~~[0213] Related compound B is also increasing with time and temperature, and now fails specification of NMT 0.1% at 40°C condition for both suspension and one solution formulation. Only formulation 2602 meets all impurity specifications.

Table 5-3: Summary of related compound B T6M results

Solution/Suspension #	25°C/60% RH	30°C/65% RH	40°C/75% RH
Solution 00	Meets specification	Meets specification	0.398%
Solution 02	Meets specification	Meets specification	Meets specification
~~Suspension 01~~	~~Meets specification~~	~~Meets specification~~	~~0.289%~~
~~Suspension 03~~	~~Meets specification~~	~~Meets specification~~	~~0.123%~~

Table 5-4: Summary of Solution 00 results

Solution 00, 70mg/mL, 65% Vitamin E	Specifications	Initial	1 month 25°C/60 %RH	1 month 30°C/65 %RH	1 month 40°C/75 %RH	3 month 25°C/60 %RH	3 month 30°C/65 %RH	3 month 40°C/75 %RH	6 month 25°C/60 %RH	6 month 30°C/65 %RH	6 month 40°C/75 %RH
Description	Yellow to orange solution	Amber solution	Amber solution	Amber solution	Amber solution	Amber solution	Amber solution	Amber solution	Amber solution	Amber solution	Amber solution

Identification – UV	Conforms to reference std. UV and RT	pass	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Assay Diazepam (%)	90.0 to 110.0%	100.1	100.3	93.9	98.8	96.3	96.9	101.2	97.5	94.6	100.6
Impurities (%) [1]											
Nordazepam	NMT 0.3%	0.005	0.01	0.014	0.019	0.013	0.013	0.013	0.013	0.013	0.013
Related Compound B	NMT 0.1%	ND	0.002	0.007	0.03	0.008	0.016	0.089	0.024	0.098	0.398
Related Compound A	NMT 0.01%	0.002	0.002	0.004	0.011	0.002	0.002	0.01	0.005	0.058	0.051
Unknown	NMT 0.1%	0.011	0.012	0.014	0.02	0.037	0.039	0.047	0.035	0.066	0.055
Total	NMT 1.0%	0.0	0.0	0.0	0.1	0.1	0.1	0.2	0.1	0.2	0.5
Microbial Limits	Meets USP {61}	pass	N/A	N/A	N/A	N/A	N/A	N/A	pass	not tested	not tested
Fill weight (g)	report results	1.108	1.105	1.111	1.112	1.109	1.109	1.113	1.103	1.111	1.109
Fill volume (ml)	report results	1.192	1.189	1.195	1.196	1.193	1.193	1.198	1.187	1.195	1.193
Spray delivered (µl)	report results	133.9	140.7	146.8	140.5	149.1	143.5	139.6	131.4	not tested	136.4
Average Spray Content (%)	report results	95.0	101.2	100.4	99.4	99.7	94.6	99.4	95.7	not tested	108.7
Viscosity (Pa*s)	report results	0.14	0.086	0.12	0.12	0.096	0.14	0.12	0.12	0.11	0.11

[1] LOQ is approximately 0.006%, LOD is approximately 0.002%. Results below LOQ are reported in this table for trending purposes.

Table 5-5: Summary of Solution 02 results

Solution 02, 70mg/mL, 65% Vitamin E	**Specifica-tions**	**Initial**	**1 month 25°C/ 60 %RH**	**1 month 30°C/ 65 %RH**	**1 month 40°C/ 75 %RH**	**3 month 25°C/ 60 %RH**	**3 month 30°C/ 65 %RH**	**3 month 40°C/ 75 %RH**	**6 month 25°C/ 60 %RH**	**6 month 30°C/ 65 %RH**	**6 month 40°C/ 75 %RH**
Description	Yellow to orange sol'n	Amber sol'n	Amber sol'n	Amber sol'n	Amber sol'n	Amber sol'n	Amber sol'n	Amber sol'n	Amber sol'n	Amber sol'n	Amber sol'n
Identification – UV	Con-forms to reference std. UV and RT	pass	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Assay Diazepam (%)	90.0 to 110.0%	100.5	94.9	96.2	103.3	98.0	97.2	99.6	97.0	94.3	100.3
Impurities (%) [1]											
Nordazepam	NMT 0.3%	0.003	0.004	0.005	0.006	0.005	0.005	0.006	0.005	0.004	0.005
Related Compound B	NMT 0.1%	ND	0.002	0.003	0.006	0.003	0.005	0.032	0.007	0.020	0.058
Related Compound A	NMT 0.01%	0.003	0.002	0.002	0.003	0.002	0.002	0.004	0.003	0.009	0.007
Unknown	NMT 0.1%	0.01	0.012	0.014	0.018	0.019	0.025	0.032	0.014	0.020	0.018
Total	NMT 1.0%	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.1	0.1
Microbial Limits	Meets USP {61}	pass	N/A	N/A	N/A	N/A	N/A	N/A	pass	not tested	not tested
Fill weight (g)	report results	1.135	1.117	1.128	1.123	1.116	1.133	1.137	1.124	1.133	1.127
Fill volume (ml)	report results	1.184	1.165	1.177	1.172	1.164	1.182	1.186	1.172	1.183	1.176
Spray delivered (µl)	report results	115.0	137.5	137.6	133.1	143.9	136.3	143.8	129.3	not tested	124.2
Average Spray Content (%)	report results	98.6	97.6	97.7	100.7	98.7	94.7	100.5	95.8	not tested	97.1
Viscosity (Pa*s)	report results	0.69	0.68	0.64	0.68	0.63	0.65	0.64	0.61	0.55	0.56

(1) LOQ is approximately 0.006%, LOD is approximately 0.002%. Results below LOQ are reported in this table for trending purposes.

~~Table 5-6: Summary of Suspension 01 results~~

~~Suspension 01, 100 mg/ml~~	~~Specifications~~	~~Initial~~	~~1 month 25°C/60 %RH~~	~~1 month 30°C/65 %RH~~	~~1 month 40°C/75 %RH~~	~~3 month 25°C/60 %RH~~	~~3 month 30°C/65 %RH~~	~~3 month 40°C/75 %RH~~	~~6 month 25°C/60 %RH~~	~~6 month 30°C/65 %RH~~	~~6 month 40°C/75 %RH~~
~~Description~~	~~Cloudy to white solution~~	~~White dispersion~~	~~White dispersion~~	~~White dispersion~~	~~White dispersion~~	~~White dispersion~~	~~White dispersion~~	~~White dispersion~~	~~White dispersion~~	~~pale yellow dispersion~~	~~yellow dispersion~~
~~Identification—UV~~	~~Conforms to reference std. UV and RT~~	~~Pass~~	~~N/A~~	~~N/A~~	~~N/A~~	~~N/A~~	~~N/A~~	~~N/A~~	~~N/A~~	~~N/A~~	~~N/A~~
~~Assay~~	~~90.0 to~~	~~102.8~~	~~102.6~~	~~100.9~~	~~104.3~~	~~101.3~~	~~101.8~~	~~103.6~~	~~100.7~~	~~104.3~~	~~99.4~~

(markup)

Diazepam (%)	110.0%										
Impurities (%) (1)											
Nordazepam	NMT 0.3%	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Related Compound B	NMT 0.1%	ND	ND	ND	0.004	ND	0.004	0.053	0.005	0.013	0.289
Related Compound A	NMT 0.01%	ND	0.01	0.02	0.034	0.026	0.036	0.08	0.038	0.046	0.157
Unknown	NMT 0.1%	0.008	0.008	0.008	0.008	0.008	0.007	0.007	0.008	0.007	0.018
Total	NMT 1.0%	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.5
Methylparaben (%)	80.0%-115.%	97.7	100.2	92.1	100.3	101.4	100.6	101.6	106.0	103.2	103.2
Propylparaben (%)	80.0% 115.0%	100.2	100.5	92.2	99.2	100.6	99	100	98.5	97.6	96.7
Microbial Limits	Meets USP (61)	Pass	N/A	N/A	N/A	N/A	N/A	N/A	pass	not tested	not tested
Fill weight (g)	report results	1.254	1.252	1.252	1.244	1.246	1.248	1.247	1.245	1.242	1.235
Fill volume (ml)	report results	1.198	1.196	1.196	1.188	1.191	1.193	1.191	1.190	1.187	1.180
Spray delivered (µl)	report results	132.5	131.2	126	123.9	137.6	137.8	136.3	140.0	not tested	137.6
Average Spray Content (%)	report results	92.2	94.2	91.1	89.9	101.5	100.4	95.3	101.8	not tested	95.94
Viscosity (Pa*s)	report results	0.0098	0.0098	0.0092	0.0090	0.0092	0.0093	0.0089	0.0082	0.0080	0.0092

(1) LOQ is approximately 0006%, LOD is approximatelyo.002%. Results below LOQ are reported in this table for trending purposes.

Table 5-7: Summary of Suspension 03 results

Suspension 03, 200mg/mL	Specifications	Initial	1 month 25°C/60%RH	1 month 30°C/65%RH	1 month 40°C/75%RH	3 month 25°C/60%RH	3 month 30°C/65%RH	3 month 40°C/75%RH	6 month 25°C/60%RH	6 month 30°C/65%RH	6 month 40°C/75%RH

Description	Cloudy to white dispersion	White dispersion	White dispersion	White dispersion	White dispersion	White dispersion	White dispersion	White dispersion	White dispersion	pale yellow dispersion	yellow dispersion
Identification – UV	Conforms to reference std. UV and RT	Pass	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Assay Diazepam (%)	90.0 to 110.0%	100.7	101.2	98.9	101.6	102.6	103.6	103.1	100.5	98.9	100.1
Impurities (%) [1]											
Nordazepam	NMT 0.3%	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Related Compound B	NMT 0.1%	ND	ND	ND	ND	0.002	ND	0.023	0.002	0.008	0.123
Related Compound A	NMT 0.01%	ND	0.005	0.01	0.017	0.017	0.012	0.039	0.019	0.029	0.081
Unknown	NMT 0.1%	0.008	0.008	0.008	0.008	0.008	0.008	0.008	0.008	0.007	0.008
Total	NMT 1.0%	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.2
Methylparaben (%)	80.0%-115.%	93.4	101.1	93.8	99.7	101.5	101.6	101.2	103.5	97.2	102.1
Propylparaben (%)	80.0% 115.0%	95.6	100.2	94	98.4	100.1	101.3	99.2	97.1	91.9	95.9
Microbial Limits	Meets USP {61}	Pass	N/A	N/A	N/A	N/A	N/A	N/A	pass	not tested	not tested
Fill weight (g)	report results	1.276	1.28	1.259	1.272	1.279	1.279	1.276	1.280	1.262	1.260
Fill volume (ml)	report results	1.186	1.19	1.171	1.183	1.19	1.19	1.187	1.190	1.173	1.172
Spray delivered (µl)	report results	112.4	137.4	134.3	119.9	138.9	139.3	134.3	149.4	not tested	138.0
Average Spray Content (%)	report results	82.8	99.3	97.3	86.7	98.6	102.3	96.2	98.2	not tested	98.7

~~Viscosity (Pa*s)~~	~~report results~~	~~0.021~~	~~0.017~~	~~0.017~~	~~0.019~~	~~0.016~~	~~0.016~~	~~0.018~~	~~0.014~~	~~0.013~~	~~0.015~~

~~(1) LOQ is approximately 0.006%, LOD is approximately 0.002%. Results below LOQ are reported in this table for trending purposes.~~

Table 5-8: Solution 00 25°C/60% RH spray content uniformity results

Sample	Weight Collected, g	Weight Actuated, g	Diazepam Recovered, mg	% Diazepam Recovered
1	0.13061	0.13259	9.59355	97.89
2	0.13217	0.13451	9.78206	99.82
3	0.12365	0.13332	8.85797	90.39
4	0.12761	0.13072	9.39720	95.89
5	0.14702	0.15216	8.91438	90.96
6	0.13414	0.13702	9.22442	94.13
7	0.12959	0.13384	9.84590	100.47
8	0.12367	0.14603	8.88093	90.62
9	0.13367	0.13425	9.92610	101.29
Average	0.13135	0.13716	9.380	95.72
St. Dev.	0.0070	0.0071	0.4309	4.3970
% RSD	5.35	5.20	4.59	4.59

Table 5-9: Solution 00 40°C/75% RH spray content uniformity results

Sample	**Weight Collected, g**	**Weight Actuated, g**	**Diazepam Recovered, mg**	**% Diazepam Recovered**
1	0.14139	0.15111	10.57237	107.88
2	0.14731	0.15146	11.62831	118.66
3	0.14489	0.14684	10.94206	111.65
4	0.14237	0.14873	11.94883	121.93
5	0.12188	0.13415	9.78103	99.81
6	0.12756	0.13047	9.78347	99.83
7	0.13549	0.13841	10.45221	106.66
8	0.12323	0.12543	9.41177	96.04
9	0.14299	0.14517	11.35701	115.89
Average	0.13635	0.14131	10.653	108.70