はグリコール、あるいはそれらの任意の組合せを備えることを特徴とする請求項３５記載の方法。

【請求項３７】

前記組成物は、医薬品有効成分、賦活剤、賦形剤、及びｐＨを調節し、組成物を緩衝し、分解を防ぎ、そして外観、匂い、又は味を改善するために用いられる薬剤からなる群から選択される、少なくとも１つの付加的成分を備えることを特徴とする請求項２０記載の方法。

【請求項３８】

前記組成物は、薬学的に許容可能なスプレー製剤中に存在することを特徴とする請求項２０記載の方法。

【請求項３９】

前記ベンゾジアゼピンが、約１ｍｇから約２０ｍｇまでの治療的に効果的な量で、投与されることを特徴とする請求項３８記載の方法。

【請求項４０】

前記医薬組成物は、約１０μＬから約２００μＬまでの量を有する薬学的に許容可能なスプレー製剤中に存在することを特徴とする請求項３９記載の方法。

【請求項４１】

前記医薬組成物の投与は、前記ベンゾジアゼピンの治療的に効果的な量の少なくとも一部を、少なくとも１つの鼻孔中に噴霧する工程を備えることを特徴とする請求項４０記載の方法。

【請求項４２】

前記医薬組成物の投与は、前記ベンゾジアゼピンの治療的に効果的な量の少なくとも一部を、夫々の鼻孔中に噴霧する工程を備えることを特徴とする請求項４０記載の方法。

【請求項４３】

前記医薬組成物の投与は、第１の量の前記医薬組成物を第１の鼻孔中に噴霧する工程と、第２の量の前記医薬組成物を第２の鼻孔中に噴霧する工程と、任意に、事前に選択した時間遅延の後、第３の量の前記医薬組成物を前記第１の鼻孔中に噴霧する工程を備えることを特徴とする請求項４２記載の方法。

【請求項４４】

任意に事前に選択した時間遅延の後、少なくとも第４の量の前記医薬組成物を前記第２の鼻孔の中へ投与する工程をさらに備えることを特徴とする請求項４３記載の方法。

【請求項４５】

前記医薬組成物の経鼻投与は、前記医薬組成物により処置可能となり得る疾患の症状の発病前又は発病後の任意の時点で開始することを特徴とする請求項４３記載の方法。

【請求項４６】

前記薬学的に許容可能な製剤は、少なくとも約０．０１％（Ｗ／Ｗ）のアルキルグリコシドを備えることを特徴とする請求項２０記載の組成物。

【請求項４７】

前記薬学的に許容可能な製剤は、約０．０１％から約１％（Ｗ／Ｗ）までのアルキルグリコシドを備えることを特徴とする請求項２１記載の医薬組成物。

【発明の詳細な説明】

【技術分野】

【０００１】

本出願は２００８年３月２８日に出願された米国の仮特許出願第６１／０４０，５５８号の３５Ｕ．Ｓ．Ｃ．§１１９（ｅ）優先権の利益を主張する。この出願の全ての内容は、それを参照することにより本出願に組み込まれる。

【０００２】

本発明は、ベンゾジアゼピン薬及びそれらの組成物の経鼻投与に関する

【背景技術】

【０００３】

限定するものではないが、ベンゾジアゼピンファミリーは、例えばジアゼパム、ロラゼパム、及びメダゼパム等の薬からなる。このファミリーの薬は、鎮静作用特性、精神安定特性及び筋弛緩特性を有するものとして認められる。これら薬は、精神安定弛緩薬及び骨格筋弛緩薬としてしばしば分類される。これらの薬は、不安定神経症、不眠症、激越、発作（例えば癲癇により引起されるもの等）、筋痙攣及び筋硬直（テタヌスにより引き起きされる）の症状、中枢神経抑制剤の継続的な乱用に関係する薬物離脱症候群、及び神経ガスへの暴露を抑制し、処置し、又は改善に有益であると考えられる。

【０００４】

ベンゾジアゼピンは、ニューロンのＧＡＢＡ$_A$受容体に結合することにより作用すると考えられ、おそらく、その受容体に形状の変化を引き起こし、ＧＡＢＡ$_A$受容体をガンマーアミノ酪酸（ＧＡＢＡ）にさらに近づきやすくしている。

【０００５】

ＧＡＢＡは、ＧＡＢＡ$_A$受容体に結合する場合、ＧＡＢＡ$_A$受容体が結合するニューロン中へのＣｌ$^-$イオン洪水を促進する抑制性の神経伝達物質である。Ｃｌ$^-$イオンの増加は、ニューロンの細胞膜を過分極させる。これは、活動電位を伝えるニューロンの能力を完全に又は実質的に減少させる。この受容体を標的とすることは、神経系を通過する過度な活動電位に起因する、例えばテタヌス及び癲癇等の多くの疾患を処置するのに有益である。

【０００６】

ベンゾジアゼピン薬の現在の製剤は、経口で、直腸に、又は非経口で投与され得る。これら及び他の製剤のタイプを利用する能力は、溶解性チャレンジ（ｃｈａｌｌｅｎｇｅ）に起因して、多くの場合大きく限定される。

【０００７】

経口投与は、いくつかの不都合に起因して次善として考慮され得る。例えば、経口投与のベンゾジアゼピン薬の血漿中の治療的関連性のある濃度を達成するのに要求される時間は、かなり長く、例えば１時間又はそれ以上である。その上、ベンゾジアゼピン薬は、肝臓を通り抜けるので、多くの量が代謝される。従って、治療的な血漿中濃度を達成するには、多い用量が必要となる。さらに、発作及び筋痙攣の特性に起因して、患者又は介護人のいずれかは、ベンゾジアゼピン薬を経口投与することが非常に困難となる。

【０００８】

静脈内投与は、しばしば高速に投与する経路を提供する。しかしながら、静脈内投与は、一般的には厳重に制御された臨床状況における訓練された医療従事者に限定される。その上、無菌が維持されなければならない。さらに、任意の薬を静脈内に投与することは、苦痛であり、そして針恐怖症に苦しむ患者にとっておそらく実質的ではない。

【０００９】

ベンゾジアゼピン薬の坐薬組成物は、作用が速やかに始まる。しかしながら、坐薬の不便さは、患者の親しい知人及び患者の専門医療介護人の非常に少ないグループ以外の誰かにより投与される場合、明らかに障害となる。

【発明の概要】

【課題を解決するための手段】

【００１０】

いくつかの実施形態において、経鼻投与用の医薬組成物は、患者の１以上の鼻粘膜への投与用の薬学的に許容可能な製剤中に、ベンゾジアゼピン薬と、約３０％から約９５％（Ｗ／Ｗ）までの量の１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、あるいはそれらの任意の組合せと、約５％から約７０％（Ｗ／Ｗ）までの量、好ましくは約１０％から約７０％（Ｗ／Ｗ）までの量の１以上のアルコール又はグリコール、あるいはそれらの任意の組合せとを備える。いくつかの実施形態において、ベンゾジアゼピン薬は、約３０％から約９５％（Ｗ／Ｗ）までの量の１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、あるいはそれらの任意の組合せ、及び約５％から約７０％（Ｗ／Ｗ）までの量、好ましくは約１０％から約７０％（Ｗ／Ｗ）ま

での量の１以上のアルコール又はグリコール、あるいはそれらの任意の組合せに溶解される。いくつかの実施形態において、ベンゾジアゼピン薬は、担体系に溶解される。いくつかの実施形態において、ベンゾジアゼピン薬の少なくとも一部は、ミクロ粒子、ナノ粒子又はそれらの組合せを含む形態である。いくつかの実施形態において、組成物は、ベンゾジアゼピンミクロ粒子、ナノ粒子、又はそれらの組合せが実質的にない。

【００１１】

いくつかの実施形態において、ベンゾジアゼピン薬は、アルプラゾラム、ブロチゾラム、クロルジアゼポキシド、クロバザム、クロナゼパム、クロラゼパム、デモキサゼパム、ジアゼパム、フルマゼニル、フルラゼパム、ハラゼパム、ミダゾラム、ノルダゼパム、メダゼパム、ニトラゼパム、オキサゼパム、メダゼパム、ロラゼパム、プラゼパム、クアゼパム、トリアゾラム、テマゼパム、ロプラゾラム、これらの任意の薬学的に許容可能な塩、及びこれらの任意の組合せからなる群から選択される。いくつかの実施形態において、ベンゾジアゼピン薬は、ジアゼパム、又はその薬学的に許容可能な塩である。いくつかの実施形態において、ベンゾジアゼピン薬は、ベンゾジアゼピンミクロ粒子、ナノ粒子、又はそれらの組合せを備える。いくつかの実施形態において、ベンゾジアゼピンナノ粒子は、約５０００ｎｍ未満の有効平均粒径を備える。いくつかの実施形態において、ベンゾジアゼピン薬は、ベンゾジアゼピンミクロ粒子、ナノ粒子、又はそれらの組合せが実質的にない。

【００１２】

いくつかの実施形態において、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノールは、α－トコフェロール、β－トコフェロール、γ－トコフェロール、δ－トコフェロール、α－トコトリエノール、β－トコトリエノール、γ－トコトリエノール、δ－トコトリエノール、トコフェルソラン、それらの任意の異性体、それらの任意のエステル、それらの任意のアナログ又は誘導体、及びそれらの任意の組合せからなる群から選択される。いくつかの実施形態において、合成トコフェロールは、ビタミンＥ　ＴＰＧＳ（ビタミンＥポリエチレングリコールコハク酸）を含み得る。いくつかの実施形態において、他方、合成トコフェロールは、例えばポリエチレングリコール等のグリコールポリマーと共有結合又は連結する（例えば２塩基酸の連結基を介して）トコフェロールを除外する。従って、いくつかの実施形態において、本明細書中に記載される組成物はビタミンＥ　ＴＰＧＳを除外する。

【００１３】

いくつかの実施形態において、１以上のアルコールは、エタノール、プロピルアルコール、ブチルアルコール、ペンタノール、ベンジルアルコール、それらの任意の異性体、又はそれらの任意の組合せからなる群から選択される。いくつかの実施形態において、１以上のグリコールは、エチレングリコール、プロピレングリコール、ブチレングリコール、ペンチレングリコール、それらの任意の異性体、及びそれらの任意の組合せからなる群から選択される。好適な実施形態において、グリコールは、グリコールポリマーを除外する。いくつかの好適な実施形態において、グリコールは、２００を超える平均分子量を備えるグリコールポリマーを除外する。いくつかの実施形態において、グリコールは、２００を超える平均分子量を備えるポリエチレングリコールを除外する。

【００１４】

いくつかの実施形態において、ベンゾジアゼピン薬は、約１ｍｇ／ｍＬから約６００ｍｇ／ｍＬまでの濃度で、担体系中に存在する。いくつかの実施形態において、ベンゾジアゼピン薬は、約１０ｍｇ／ｍＬから約２５０ｍｇ／ｍＬまでの濃度で、担体系中に存在する。いくつかの実施形態において、ベンゾジアゼピンは、約２０ｍｇ／ｍＬから約５０ｍｇ／ｍＬまでの濃度で、担体系中に存在する。

【００１５】

いくつかの実施形態において、担体系は、約４５％から約８５％（Ｗ／Ｗ）までの量の、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、あるいはそれらの任意の組合せを備える。いくつかの実施形態において、担体系は、約６０％か

ら約７５％（Ｗ／Ｗ）までの量の、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、あるいはそれらの任意の組合せを備える。いくつかの実施形態において、担体系は、約７０％（Ｗ／Ｗ）の量の、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、あるいはそれらの任意の組合せを備える。

【００１６】

いくつかの実施形態において、担体系は、約１０％から約７０％（Ｗ／Ｗ）の量の、１以上のアルコール又はグリコール、あるいはそれらの任意の組合せを備える。いくつかの実施形態において、担体系は、約１５％から約５５％（Ｗ／Ｗ）の量の、１以上のアルコール又はグリコール、あるいはそれらの任意の組合せを備える。いくつかの実施形態において、担体系は、約２５％から約４０％（Ｗ／Ｗ）の量の、１以上のアルコール又はグリコール、あるいはそれらの任意の組合せを備える。いくつかの実施形態において、担体系は、約３０％（Ｗ／Ｗ）の量の、１以上のアルコール又はグリコール、あるいはそれらの任意の組合せ備える。

【００１７】

いくつかの実施形態において、組成物は、医薬品有効成分、賦活剤、賦形剤、及びｐＨを調整し、組成物を緩衝し、分解を防ぎ、そして外観、匂い、又は味を改善するために用いられる剤からなる群から選択される少なくとも１つの付加的な成分を備える。

【００１８】

いくつかの実施形態において、組成物は、１以上の追加の賦形剤、例えば１以上のパラベン、１以上のポビドン、及び／又は１以上のアルキルグリコシドを備える。

【００１９】

本発明は、また、ベンゾジアゼピン薬で治療可能な疾患のある患者を処置する方法を開示する。いくつかの実施形態において、患者はヒトである。いくつかの実施形態において、方法は、ベンゾジアゼピン薬を含む経鼻投与用の医薬組成物と、約３０％から約９５％（Ｗ/Ｗ）までの量の、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、あるいはそれらの任意の組合せと、及び約５％から約７０％（Ｗ/Ｗ）までの量、好ましくは約１０％から約７０％（Ｗ／Ｗ）までの量の１以上のアルコール又はグリコール、あるいはそれらの任意の組合せとを患者の１以上の鼻粘膜に投与する工程を含む。いくつかの実施形態において、ベンゾジアゼピンは、約３０％から約９５％（Ｗ／Ｗ）までの量の１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、あるいはそれらの任意の組合せ、及び約５％から約７０％までの量、好ましくは約１０％から約７０％（Ｗ／Ｗ）までの量の１以上のアルコール又はグリコール、あるいはそれらの任意の組合せに溶解される。いくつかの実施形態において、ベンゾジアゼピン薬は、担体系に溶解される。いくつかの実施形態において、ベンゾジアゼピン薬は、ベンゾジアゼピンミクロ粒子、ナノ粒子又はそれらの組合せを含む。いくつかの実施形態において、組成物は、ベンゾジアゼピンミクロ粒子、ナノ粒子、又はそれらの組合せが実質的にない。

【００２０】

いくつかの実施形態において、ベンゾジアゼピン薬は、アルプラゾラム、ブロチゾラム、クロルジアゼポキシド、クロバザム、クロナゼパム、クロラゼパム、デモキサゼパム、ジアゼパム、フルマゼニル、フルラゼパム、ハラゼパム、ミダゾラム、ノルダゼパム、メダゼパム、ニトラゼパム、オキサゼパム、メダゼパム、ロラゼパム、プラゼパム、クアゼパム、トリアゾラム、テマゼパム、ロプラゾラム、又はこれらの任意の薬学的に許容可能な塩、及びこれらの任意の組合せからなる群から選択される。いくつかの実施形態において、ベンゾジアゼピン薬は、ジアゼピン又はその任意の薬学的に許容可能な塩である。いくつかの実施形態において、ベンゾジアゼピン薬は、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール並びに１以上のアルコール又はグリコールを含む単相に完全に溶解される。いくつかの実施形態において、ベンゾジアゼピン薬は、ベンゾジアゼピンミクロ粒子、ナノ粒子、又はそれらの組合せを備える。いくつかの実施形態において、組成物は、さらに水を備える。いくつかのこのような実施形態において、ベン

ゾジアゼピンナノ粒子は、約５０００ｎｍ未満の有効平均粒径を備える。いくつかの実施形態において、組成物は、ベンゾジアゼピンミクロ粒子、ナノ粒子、又はそれらの組合せが実質的にない。

【００２１】

いくつかの実施形態において、１以上の天然又は合成トコフェロール又は天然又は合成トコトリエノールは、α－トコフェロール、β－トコフェロール、γ－トコフェロール、δ－トコフェロール、α－トコトリエノール、β－トコトリエノール、γ－トコトリエノール、δ－トコトリエノール、トコフェルソラン、それらの任意の異性体、それらの任意のエステル、それらの任意のアナログ又は誘導体、及びそれらの任意の組合せからなる群から選択される。

【００２２】

いくつかの実施形態において、１以上のアルコールは、エタノール、プロピルアルコール、ブチルアルコール、ペンタノール、ベンジルアルコール、それらの任意の異性体、及びそれらの任意の組合せからなる群から選択される。いくつかの実施形態において、１以上のグリコールは、エチレングリコール、プロピレングリコール、ブチレングリコール、ペンチレングリコール、それらの任意の異性体、及びそれらの任意の組合せからなる群から選択される。いくつかの実施形態において、アルコール又はグリコールは水がない（無水、ＵＳＰ）。いくつかの実施形態において、アルコールはエタノールである（無水、ＵＳＰ）。

【００２３】

いくつかの実施形態において、ベンゾジアゼピン薬は担体系中に、約１ｍｇ／ｍＬから約６００ｍｇ／ｍＬまでの濃度で存在する。いくつかの実施形態において、ベンゾジアゼピン薬は担体系中に、約１０ｍｇ／ｍＬから約２５０ｍｇ／ｍＬまでの濃度で存在する。いくつかの実施形態において、ベンゾジアゼピン薬は担体系中に、約２０ｍｇ／ｍＬから約５０ｍｇ／ｍＬまでの濃度で存在する。

【００２４】

いくつかの実施形態において、担体系は、約４５％から約８５％（Ｗ／Ｗ）までの量の、１以上の天然又は合成トコフェロール又は天然又は合成トコトリエノール、あるいはそれらの任意の組合せを備える。いくつかの実施形態において、担体系は、約６０％から約７５％（Ｗ／Ｗ）までの量の、１以上の天然又は合成トコフェロール又は天然又は合成トコトリエノール、あるいはそれらの任意の組合せを備える。いくつかの実施形態において、担体系は、約７０％（Ｗ／Ｗ）の量の、１以上の天然又は合成トコフェロール又は天然又は合成トコトリエノール、あるいはそれらの任意の組合せを備える。

【００２５】

いくつかの実施形態において、担体系は、約１５％から約５５％（Ｗ／Ｗ）までの量の、１以上のアルコール又はグリコール、あるいはそれらの任意の組合せを備える。いくつかの実施形態において、担体系は約２５％から約４０％（Ｗ／Ｗ）の量の、１以上のアルコール又はグリコール、あるいはそれらの任意の組合せを備える。いくつかの実施形態において、担体系は約３０％（Ｗ／Ｗ）の量の、１以上のアルコール又はグリコール、あるいはそれらの任意の組合せ備える。

【００２６】

いくつかの実施形態において、組成物は、医薬品有効成分、賦活剤、賦形剤、及びｐＨを調節し、組成物を緩衝し、分解を防ぎ、そして外観、匂い、又は味を改善するために用いられる薬剤からなる群から選択される少なくとも１つの付加的成分を備える。

【００２７】

いくつかの実施形態において、組成物は、薬学的に許容可能なスプレー製剤中に存在し、さらに、１以上の患者の鼻粘膜に組成物を投与することを備える。いくつかの実施形態において、治療的に効果的な量は、約１ｍｇから約２０ｍｇまでのベンゾジアゼピンである。いくつかの実施形態において、医薬組成物は、約１０μＬから約２００μＬまでの量を有する薬学的に許容可能なスプレー製剤中に存在する。

【００２８】
いくつかの実施形態において、組成物の投与は、組成物の治療的に効果的な量の少なくとも一部を、少なくとも１つの鼻孔中に噴霧する工程を備える。いくつかの実施形態において、組成物の投与は、組成物の治療学的に効果的な量の少なくとも一部を、それぞれの鼻孔中に噴霧する工程を備える。いくつかの実施形態において、組成物の投与は、第１の量の組成物を、第１の鼻孔中に噴霧する工程と、第２の量の組成物を第２の鼻孔中に噴霧する工程と、任意に、事前に選択した時間遅延の後、第３の量の組成物を第１の鼻孔中に噴霧する工程を備える。いくつかの実施形態は、任意に事前に選択した時間遅延の後、少なくとも第４の量の組成物を第２の鼻孔の中へ投与する工程をさらに備える。
【００２９】
いくつかの実施形態において、組成物の投与は、組成物により処置可能となり得る疾患の症状の発病前又は発病後の任意の時点で開始する。
【００３０】
本発明の追加の実施形態、使用、及び効果は、本明細書中に記載される開示の考察に基づき、当該分野の当業者にとって明らかである。
【発明を実施するための形態】
【００３１】
本明細書中に言及される、全ての出版物、特許、及び特許出願は、それぞれの個別の出版物、特許、又は特許出願が、特に及び個別に、参照により組み込まれるものと示された場合と同様の程度に、参照されることにより本明細書中に組み込まれるものとする。
【００３２】
本明細書中に提供されるのは、１以上のベンゾジアゼピン薬の医薬組成物及び、このような医薬組成物を用いる方法である。このような医薬組成物は経鼻的に投与される。
【００３３】
いくつかの実施形態において、経鼻投与用の医薬組成物は、患者の１以上の鼻粘膜への投与用の薬学的に許容可能な製剤中に、ベンゾジアゼピン薬と、約３０％から約９５％（Ｗ／Ｗ）までの量の、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、あるいはそれらの任意の組合せと、約１０％から約７０％（Ｗ／Ｗ）までの量の、１以上のアルコール又はグリコール、あるいはそれらの任意の組合せとを備える。いくつかの実施形態においてベンゾジアゼピン薬は、約３０％から約９５％（Ｗ／Ｗ）までの量の、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、あるいはそれらの任意の組合せと、約１０％から約７０％（Ｗ／Ｗ）までの量の１以上のアルコール又はグリコール、あるいはそれらの任意の組合せとに溶解される。いくつかの実施形態において、ベンゾジアゼピン薬は、担体系に溶解される。いくつかの実施形態において、ベンゾジアゼピン薬の少なくとも一部は、ミクロ粒子、ナノ粒子、又はそれらの組合せの形態である。いくつかの実施形態において組成物には、ベンゾジアゼピンミクロ粒子、ナノ粒子、又はそれらの組合せが実質的にない。
【００３４】
いくつかの実施形態において、経鼻投与用の医薬組成物は、患者の１以上の鼻粘膜への投与用の薬学的に許容可能な製剤中に、ベンゾジアゼピン薬と、約３０％から約９５％（Ｗ／Ｗ）までの量の、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、あるいはそれらの任意の組合せと、約５％から約７０％（Ｗ／Ｗ）までの量の、１以上のアルコール又はグリコール、あるいはそれらの任意の組合せとを備える。いくつかの実施形態においてベンゾジアゼピン薬は、約３０％から約９５％（Ｗ／Ｗ）までの量の、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、あるいはそれらの任意の組合せと、約５％から約７０％（Ｗ／Ｗ）までの量の１以上のアルコール又はグリコール、あるいはそれらの任意の組合せとに溶解される。いくつかの実施形態において、ベンゾジアゼピン薬は、担体系に溶解される。いくつかの実施形態において、ベンゾジアゼピン薬の少なくとも一部は、ミクロ粒子、ナノ粒子、又はそれらの組合せの形態である。いくつかの実施形態において組成物には、ベンゾジアゼピンミクロ粒

子、ナノ粒子、又はそれらの組合せが実質的にない。

【００３５】

いくつかの実施形態において、ベンゾジアゼピン薬は、アルプラゾラム、ブロチゾラム、クロルジアゼポキシド、クロバザム、クロナゼパム、クロラゼパム、デモキサゼパム、ジアゼパム、フルマゼニル、フルラゼパム、ハラゼパム、ミダゾラム、ノルダゼパム、メダゼパム、ニトラゼパム、オキサゼパム、メダゼパム、ロラゼパム、プラゼパム、クアゼパム、トリアゾラム、テマゼパム、ロプラゾラム、これらの任意の薬学的に許容可能な塩、及びこれらの任意の組合せから成る群から選択される。いくつかの実施形態において、ベンゾジアゼピン薬は、ジアゼパム、又はその薬学的に許容可能な塩である。いくつかの実施形態において、ベンゾジアゼピン薬は、ベンゾジアゼピンミクロ粒子、ナノ粒子、又はそれらの組合せを備える。いくつかの実施形態において、ベンゾジアゼピンナノ粒子は、約５０００ｎｍ未満の有効平均粒径を有する。いくつかの実施形態において、組成物は、ベンゾジアゼピンミクロ粒子、ナノ粒子、又はそれらの組合せが実質的にない。

【００３６】

いくつかの実施形態において、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノールは、α－トコフェロール、β－トコフェロール、γ－トコフェロール、δ－トコフェロール、α－トコトリエノール、β－トコトリエノール、γ－トコトリエノール、δ－トコトリエノール、トコフェルソラン（ｔｏｃｏｐｈｅｒｓｏｌａｎ）、それらの任意の異性体、それらの任意のエステル、それらの任意のアナログ又は誘導体、及びそれらの任意の組合せから成る群から選択される。いくつかの実施形態において、担体系は、ビタミンＥ　ＴＰＧＳなどの、トコフェロールコアと共有結合又は連結するグリコールポリマーを有する、１以上の合成トコフェロールを含み、このことは米国特許第６，１９３，９８５号に記載されており、これは全体として参照することにより本明細書中に組み込まれる。特に、ベンゾジアゼピンがトコフェロールの相には溶解していない、いくつかのベンゾジアゼピンの粒子懸濁液中では、ビタミンＥ　ＴＰＧＳが、粒子（ミクロ粒子、ナノ粒子、又は組合せ）の懸濁液を安定させるための所望の賦形剤であり得るということが見出されている。いくつかの実施形態において、他方では、担体系は、ビタミンＥ　ＴＰＧＳなどの、トコフェロールコアと共有結合又は連結するグリコールポリマーを有する合成トコフェロールを特に除外し、このことは米国特許第６，１９３，９８５号に記載されており、これは全体として参照することにより本明細書中に組み込まれる。

【００３７】

いくつかの実施形態において、１以上のアルコールは、エタノール、プロピルアルコール、ブチルアルコール、ペンタノール、ベンジルアルコール、それらの任意の異性体、又はそれらの任意の組合せから成る群から選択される。いくつかの実施形態において、アルコールはエタノール（無水、ＵＳＰ）である。いくつかの実施形態において、１以上のグリコールは、エチレングリコール、プロピレングリコール、ブチレングリコール、ペンチレングリコール、それらの任意の異性体、及びそれらの任意の組合せから成る群から選択される。いくつかの実施形態において、グリコールはプロピレングリコールＵＳＰである。いくつかの実施形態において、合成トコフェロールはビタミンＥ　ＴＰＧＳ（ビタミンＥポリエチレングリコールスクシネート）を含むことができる。いくつかの実施形態において、他方では、合成トコフェロールは、ポリエチレングリコールなどのグリコールポリマーと（例えば２塩基酸の連結基を介して）共有結合又は連結するトコフェロールを除外する。従って、いくつかの実施形態において、本明細書中に記載の組成物はビタミンＥ　ＴＰＧＳを除外する。

【００３８】

いくつかの実施形態において、ベンゾジアゼピン薬は担体系中に、約１ｍｇ／ｍＬから約６００ｍｇ／ｍＬまでの濃度で存在する。いくつかの実施形態において、ベンゾジアゼピン薬は担体系中に、約１０ｍｇ／ｍＬから約２５０ｍｇ／ｍＬまでの濃度で存在する。いくつかの実施形態において、ベンゾジアゼピン薬は担体系中に、約２０ｍｇ／ｍＬから約５０ｍｇ／ｍＬまでの濃度で存在する。

【００３９】
いくつかの実施形態において、担体系は、約４５％から約８５％（Ｗ／Ｗ）までの量の、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、あるいはそれらの任意の組合せを備える。いくつかの実施形態において、担体系は、約６０％から約７５％（Ｗ／Ｗ）までの量の、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、あるいはそれらの任意の組合せを備える。いくつかの実施形態において、担体系は、約７０％（Ｗ／Ｗ）の量の、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、あるいはそれらの任意の組合せを備える。いくつかの実施形態において、合成トコフェロールはビタミンＥ　ＴＰＧＳ（ビタミンＥポリエチレングリコールスクシネート）を含むことができる。いくつかの実施形態において、他方では、合成トコフェロールは、ポリエチレングリコールなどのグリコールポリマーと（例えば２塩基酸の連結基を介して）共有結合又は連結するトコフェロールを除外する。従って、いくつかの実施形態において、本明細書中に記載の組成物はビタミンＥ　ＴＰＧＳを除外する。

【００４０】
いくつかの実施形態において、担体系は１以上のアルコール又はグリコール、あるいはそれらの任意の組合せを、約１０％から約５５％まで、約１０％から約４０％まで、約１０％から約３５％まで、約１２％から約５５％まで、約１２％から約４０％まで、約１２％から約３５％まで、約１５％から約５５％まで、約１５％から約４０％まで、約１５％から約３５％まで、約１０％、約１２．５％、約１５％、約１７．５％、約２０％、約２２．５％、約２５％、約２７．５％、約３０％、約３２．５％、約３５％、約３７．５％、約４０％、約４２．５％、約４５％、約４７．５％、約５０％、約５２．５％、又は約５５％（Ｗ／Ｗ）の量で備える。いくつかの実施形態において、担体系は約２５％から約４０％（Ｗ／Ｗ）の量の、１以上のアルコール又はグリコール、あるいはそれらの任意の組合せを備える。いくつかの実施形態において、担体系は約３０％（Ｗ／Ｗ）の量の、１以上のアルコール又はグリコール、あるいはそれらの任意の組合せを備える。いくつかの実施形態において、アルコールはエタノールである、又はエタノールを含有する。いくつかの好ましい実施形態において、グリコールはグリコールポリマーを除外する。いくつかの好ましい実施形態において、グリコールは２００より大きい平均分子量を有するグリコールポリマーを除外する。いくつかの実施形態において、グリコールは約２００より大きい平均分子量を有するポリエチレングリコールを除外する。

【００４１】
いくつかの実施形態において、担体系は、約１５％から約５５％（Ｗ／Ｗ）の量の、１以上のアルコール又はグリコール、あるいはそれらの任意の組合せを備える。いくつかの実施形態において、担体系は約２５％から約４０％（Ｗ／Ｗ）の量の、１以上のアルコール又はグリコール、あるいはそれらの任意の組合せを備える。いくつかの実施形態において、担体系は約３０％（Ｗ／Ｗ）の量の、１以上のアルコール又はグリコール、あるいはそれらの任意の組合せ備える。

【００４２】
いくつかの実施形態において、組成物は、医薬品有効成分、賦活剤、賦形剤、及びｐＨを調整し、組成物を緩衝し、分解を防ぎ、そして外観、匂い、又は味を改善するために用いられる剤から成る群から選択される少なくとも１つの付加的な成分を備える。

【００４３】
いくつかの実施形態において、組成物は少なくとも１つのアルキルグリコシドを備える。いくつかの実施形態において、少なくとも１つのアルキルグリコシドは、米国特許第５，６６１，１３０号に記載のものであり、これは参照することにより本明細書中に組み込まれる。

【００４４】
いくつかの実施形態において、組成物は、天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、及びアルコール又はグリコールを備える溶媒中に完全に溶解し

ているベンゾジアゼピン薬を備える。いくつかの実施形態において、組成物は、天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、及びアルコール又はグリコールを備える溶媒中に完全に溶解しているベンゾジアゼピン薬を備え、そこで溶液は実質的に水がない。（いくつかの実施形態において、「実質的に水がない」とは、溶液が約１％未満、約０．５％未満、約０．２５％未満、又は約０．１％未満の水を含有することを示す。）いくつかの実施形態において、組成物は、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、１以上のアルコール又はグリコール、及び任意に１以上のアルキルグリコシドから成る溶媒中に完全に溶解している、ベンゾジアゼピン薬から必須のものとして構成される。いくつかの実施形態において、組成物は、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、１以上のアルコール又はグリコール、及び任意に１以上のアルキルグリコシドから成る溶媒中に完全に溶解している、ベンゾジアゼピン薬から必須のものとして構成され、そこで溶液は少なくとも実質的に水がない。（いくつかの実施形態において、「実質的に水がない」とは、溶液が約１％未満、約０．５％未満、約０．２５％未満、又は約０．１％未満の水を含有することを示す。）いくつかの実施形態において、組成物は、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、１以上のアルコール又はグリコール、及び任意に１以上のアルキルグリコシドから成る溶媒中に溶解している、ベンゾジアゼピンから構成される。いくつかの実施形態において、組成物は、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、１以上のアルコール又はグリコール、及び任意に１以上のアルキルグリコシドから成る溶媒中に溶解している、ベンゾジアゼピンから構成され、そこで溶液は少なくとも実質的に水がない。（いくつかの実施形態において、「実質的に水がない」とは、溶液が約１％未満、約０．５％未満、約０．２５％未満、又は約０．１％未満の水を含有することを示す。）

【００４５】

いくつかの実施形態において、組成物は、天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、及びアルコール又はグリコールを有する溶媒中に完全に溶解しているベンゾジアゼピン薬を備える。従って、いくつかの実施形態において、組成物は、ベンゾジアゼピンミクロ粒子、ナノ粒子、又はそれらの組合せが実質的にない。いくつかの実施形態において、組成物は、天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、及びアルコール又はグリコールを有する溶媒中に完全に溶解しているベンゾジアゼピン薬を備え、そこで溶液は少なくとも実質的に水がない。（いくつかの実施形態において、「実質的に水がない」とは、溶液が約１％未満、約０．５％未満、約０．２５％未満、又は約０．１％未満の水を含有することを示す。）いくつかの実施形態において、組成物は、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、１以上のアルコール又はグリコール、及び任意に１以上のアルキルグリコシドから成る溶媒中に完全に溶解している、ベンゾジアゼピン薬から必須のものとして構成される。いくつかの実施形態において、組成物は、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、１以上のアルコール又はグリコール、及び任意に１以上のアルキルグリコシドから成る溶媒中に完全に溶解している、ベンゾジアゼピン薬から必須のものとして構成され、そこで溶液は少なくとも実質的に水がない。（いくつかの実施形態において、「実質的に水がない」とは、溶液が約１％未満、約０．５％未満、約０．２５％未満、又は約０．１％未満の水を含有することを示す。）いくつかの実施形態において、組成物は、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、１以上のアルコール又はグリコール、及び任意に１以上のアルキルグリコシドから成る溶媒中に溶解している、ベンゾジアゼピンから構成される。いくつかの実施形態において、組成物は、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、１以上のアルコール又はグリコール、及び任意に１以上のアルキルグリコシドから成る溶媒中に溶解している、ベンゾジアゼピンから構成され、そこで溶液は少なくとも実質的に水がない。（いくつかの実施形態において、「実質的に水がない」とは、溶液が約１％未満、約０．５％未満、約０．２５％未満、又は約０．１％未満の水を含有す

ることを示す。）

【００４６】

いくつかの実施形態において、組成物は、天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、及び１以上のアルコール又はグリコールを含有する担体系中に、少なくとも部分的に微粒子型で懸濁したベンゾジアゼピン薬を含有する。いくつかの実施形態において、実質的に全てのベンゾジアゼピン薬は微粒子形態である。いくつかの実施形態において、ベンゾジアゼピン薬の少なくとも一部はミクロ粒子又はナノ粒子の形態である。担体系は、その中で組成物中に存在する少なくとも１つのベンゾジアゼピンの量が、担体系中のその溶解性を超えるものである。いくつかの実施形態において、このような組成物中の担体系は水を含む。いくつかの実施形態において、このような液体担体系は、水及び１以上の賦形剤を含有する。いくつかの実施形態において、１以上の賦形剤は、担体系中に溶解又は懸濁されている。いくつかの実施形態において、少なくとも１つのこのような賦形剤は、担体系中のベンゾジアゼピンの粒子の懸濁液を安定させる。いくつかの実施形態において、担体系は様々な濃度のパラベン（例えば、メチルパラベン、プロピルパラベン等）、及び／又は、ポビドン（ポリビニルピロリドン）などの、様々な量の１以上の界面活性剤を含有し得る。いくつかの実施形態において、ベンゾジアゼピンの粒子懸濁液は、ポリエチレングリコールなどの、１以上のグリコール重合体を特に除外する。いくつかの実施形態において、ベンゾジアゼピンの粒子懸濁液は、２００ｇ／ｍｏｌより大きい分子量を有する、１以上のグリコール重合体を特に除外する。いくつかの実施形態において、組成物は、合成トコフェロール、１以上のパラベン、１以上のアルコール又はグリコール、１以上の界面活性剤及び水を備える担体系中に懸濁されたベンゾジアゼピンのミクロ粒子及び／又はナノ粒子を含む形態におけるベンゾジアゼピン薬を備える。いくつかの実施形態において、組成物はビタミンＥ　ＴＰＧＳ、メチルパラベンとプロピルパラベンの１もしくは両方、少なくとも１つのグリコール、ポビドン及び水を備える担体系中に懸濁されたベンゾジアゼピンのミクロ粒子及び／又はナノ粒子を含む形態におけるベンゾジアゼピン薬を備える。いくつかの実施形態において、組成物はビタミンＥ　ＴＰＧＳ、メチルパラベン、プロピルパラベン、プロピレングリコール、ポビドン及び水を備える担体系中に懸濁されたベンゾジアゼピンのミクロ粒子及び／又はナノ粒子を含む形態におけるベンゾジアゼピン薬を備える。いくつかの実施形態において、組成物は合成トコフェロール、１以上のパラベン、１以上のアルコール又はグリコール、１以上の界面活性剤及び水から必須のものとして構成される担体系中に懸濁されたベンゾジアゼピンのミクロ粒子及び／又はナノ粒子を含む形態におけるベンゾジアゼピン薬から必須のものとして構成される。いくつかの実施形態において、組成物はビタミンＥ　ＴＰＧＳ、メチルパラベンとプロピルパラベンの１もしくは両方、少なくとも１つのグリコール、ポビドン及び水から必須のものとして構成される担体系中に懸濁されたベンゾジアゼピンのミクロ粒子及び／又はナノ粒子を含む形態におけるベンゾジアゼピン薬から必須のものとして構成される。いくつかの実施形態において、組成物はビタミンＥ　ＴＰＧＳ、メチルパラベン、プロピルパラベン、プロピレングリコール、ポビドン及び水から必須のものとして成される担体系中に懸濁されたベンゾジアゼピンのミクロ粒子及び／又はナノ粒子を含む形態におけるベンゾジアゼピン薬から必須のものとして構成される。いくつかの実施形態において、組成物は合成トコフェロール、１以上のパラベン、１以上のアルコール又はグリコール、１以上の界面活性剤及び水から構成される担体系中に懸濁されたベンゾジアゼピンのミクロ粒子及び／又はナノ粒子を含む形態におけるベンゾジアゼピン薬から構成される。いくつかの実施形態において、組成物はビタミンＥ　ＴＰＧＳ、メチルパラベンとプロピルパラベンの１もしくは両方、少なくとも１つのグリコール、ポビドン及び水から構成される担体系中に懸濁されたベンゾジアゼピンのミクロ粒子又はナノ粒子を含む形態におけるベンゾジアゼピン薬から構成される。いくつかの実施形態において、組成物はビタミンＥ　ＴＰＧＳ、メチルパラベン、プロピルパラベン、プロピレングリコール、ポビドン及び水から構成される担体系中に懸濁されたベンゾジアゼピンのミクロ粒子及び／又はナノ粒子を含む形態におけるベンゾジアゼピン薬から構成される。

【００４７】
いくつかの実施形態において、組成物は、天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、１以上のアルコール又はグリコール、及びアルキルグリコシドを含有する担体系中に、少なくとも部分的に微粒子型で懸濁されたベンゾジアゼピン薬を含有する。いくつかの実施形態において、実質的に全てのベンゾジアゼピン薬は微粒子型である。いくつかの実施形態において、ベンゾジアゼピン薬の少なくとも一部はミクロ粒子又はナノ粒子の形態である。担体系は、その中で組成物中に存在する少なくとも１つのベンゾジアゼピンの量が、担体系中のその溶解性を超えるものである。いくつかの実施形態において、このような組成物中の担体系は水を含む。いくつかの実施形態において、このような液体担体系は、水及び１以上の賦形剤を含有する。いくつかの実施形態において、１以上の賦形剤は、担体系中に溶解又は懸濁されている。いくつかの実施形態において、少なくとも１つのこのような賦形剤は、担体系中のベンゾジアゼピンの粒子の懸濁液を安定させる。いくつかの実施形態において、担体系は様々な濃度のパラベン（例えば、メチルパラベン、プロピルパラベン等）、及び／又は、ポビドン（ポリビニルピロリドン）などの、様々な量の１以上の界面活性剤を含有し得る。いくつかの実施形態において、ベンゾジアゼピンの粒子懸濁液は、ポリエチレングリコールなどの、１以上のグリコール重合体を特に除外する。いくつかの実施形態において、ベンゾジアゼピンの粒子懸濁液は、２００ｇ／ｍｏｌより大きい分子量を有する、１以上のグリコール重合体を特に除外する。いくつかの実施形態において、組成物は、合成トコフェロール、１以上のパラベン、１以上のアルコール又はグリコール、アルキルグリコシド及び水を備える担体系中に懸濁されたベンゾジアゼピンのミクロ粒子及び／又はナノ粒子を含む形態におけるベンゾジアゼピン薬を備える。いくつかの実施形態において、組成物はビタミンＥ　ＴＰＧＳ、メチルパラベンとプロピルパラベンの１もしくは両方、少なくとも１つのグリコール、アルキルグリコシド及び水を備える担体系中に懸濁されたベンゾジアゼピンのミクロ粒子及び／又はナノ粒子を含む形態におけるベンゾジアゼピン薬を備える。いくつかの実施形態において、組成物はビタミンＥ　ＴＰＧＳ、メチルパラベン、プロピルパラベン、プロピレングリコール、アルキルグリコシド及び水を備える担体系中に懸濁されたベンゾジアゼピンのミクロ粒子及び／又はナノ粒子を含む形態におけるベンゾジアゼピン薬を備える。いくつかの実施形態において、組成物は合成トコフェロール、１以上のパラベン、１以上のアルコール又はグリコール、アルキルグリコシド、任意に界面活性剤及び水から必須のものとして構成される担体系中に懸濁されたベンゾジアゼピンのミクロ粒子及び／又はナノ粒子を含む形態におけるベンゾジアゼピン薬から必須のものとして構成される。いくつかの実施形態において、組成物はビタミンＥ　ＴＰＧＳ、メチルパラベンとプロピルパラベンの１もしくは両方、少なくとも１つのグリコール、アルキルグリコシド、任意にポビドン及び水から必須のものとして構成される担体系中に懸濁されたベンゾジアゼピンのミクロ粒子又はナノ粒子を含む形態におけるベンゾジアゼピン薬から必須のものとして構成される。いくつかの実施形態において、組成物はビタミンＥ　ＴＰＧＳ、メチルパラベン、プロピルパラベン、プロピレングリコール、アルキルグリコシド、任意にポビドン及び水から基本的に構成される担体系中に懸濁されたベンゾジアゼピンのミクロ粒子及び／又はナノ粒子を含む形態におけるベンゾジアゼピン薬から必須のものとして構成される。いくつかの実施形態において、組成物は合成トコフェロール、１以上のパラベン、１以上のアルコール又はグリコール、アルキルグリコシド、任意に１以上の界面活性剤、及び水から構成される担体系中に懸濁されたベンゾジアゼピンのミクロ粒子及び／又はナノ粒子を含む形態におけるベンゾジアゼピン薬から構成される。いくつかの実施形態において、組成物はビタミンＥ　ＴＰＧＳ、メチルパラベンとプロピルパラベンの１もしくは両方、少なくとも１つのグリコール、アルキルグリコシド、任意にポビドン及び水から構成される担体系中に懸濁されたベンゾジアゼピンのミクロ粒子又はナノ粒子を含む形態におけるベンゾジアゼピン薬から構成される。いくつかの実施形態において、組成物はビタミンＥ　ＴＰＧＳ、メチルパラベン、プロピルパラベン、プロピレングリコール、アルキルグリコシド、任意にポビドン及び水から構成される担体系中に懸濁されたベンゾジアゼピンのミクロ粒

子及び／又はナノ粒子を含む形態におけるベンゾジアゼピン薬から構成される。

【００４８】

本発明はまた、ベンゾジアゼピン薬を用いて処置可能であり得る疾患の患者を処置する方法を開示する。いくつかの実施形態において、患者はヒトである。いくつかの実施形態において、方法は、ベンゾジアゼピン薬を備える経鼻投与用の医薬組成物と、約３０％から約９５％（Ｗ／Ｗ）までの量の、１またはそれより多い天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、又はそれらの任意の組合せと、約５％から約７０％（Ｗ／Ｗ）までの量の、好ましくは約１０％から約７０％（Ｗ／Ｗ）までの量の、１又はそれより多いアルコール又はグリコール、又はそれらの任意の組合せとを、患者の１以上の鼻粘膜に投与する工程を備える。いくつかの実施形態において、ベンゾジアゼピンは約３０％から約９５％（Ｗ／Ｗ）までの量の、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、あるいはそれらの任意の組合せと、約５％から約７０％（Ｗ／Ｗ）までの量の、好ましくは約１０％から約７０％（Ｗ／Ｗ）までの量の、１以上のアルコール又はグリコール、あるいはそれらの任意の組合せの中に溶解される。いくつかの実施形態において、ベンゾジアゼピン薬は担体系中に溶解される。他の実施形態において、ベンゾジアゼピン薬の少なくとも一部はミクロ粒子、ナノ粒子、又はそれらの組合せを含む形態である。いくつかの実施形態において、組成物は実質的にベンゾジアゼピンのミクロ粒子、ナノ粒子、又はそれらの組合せがない。

【００４９】

いくつかの実施形態において、ベンゾジアゼピン薬は、アルプラゾラム、ブロチゾラム、クロルジアゼポキシド、クロバザム、クロナゼパム、クロラゼパム、デモキサゼパム、ジアゼパム、フルマゼニル、フルラゼパム、ハラゼパム、ミダゾラム、ノルダゼパム、メダゼパム、ニトラゼパム、オキサゼパム、メダゼパム、ロラゼパム、プラゼパム、クアゼパム、トリアゾラム、テマゼパム、ロプラゾラム、又はこれらの薬学的に許容可能な任意の塩、及びこれらの任意の組合せから成る群から選択される。いくつかの実施形態において、ベンゾジアゼピン薬は、ジアゼパム、又はその薬学的に許容可能な塩である。いくつかの実施形態において、ベンゾジアゼピン薬は、ベンゾジアゼピンミクロ粒子、ナノ粒子、又はそれらの組合せを備える。いくつかの実施形態において、ベンゾジアゼピンナノ粒子は、約５０００ｎｍ未満の有効平均粒径を有する。

【００５０】

いくつかの実施形態において、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノールは、α－トコフェロール、β－トコフェロール、γ－トコフェロール、δ－トコフェロール、α－トコトリエノール、β－トコトリエノール、γ－トコトリエノール、δ－トコトリエノール、トコフェルソラン、それらの任意の異性体、それらの任意のエステル、それらの任意のアナログ又は誘導体、及びそれらの任意の組合せから成る群から選択される。合成トコフェロールは、ポリエチレングリコール基などの親水基を含むよう修飾されたトコフェロールを含み得、２塩基酸などの共有結合性の連結基を介してトコフェロールと共有結合あるいはトコフェロールと連結し得る。この型の例示的な合成トコフェロールは、当該分野の当業者は、同様の二塩基酸及び／又は親水基を有する他の合成トコフェロールを想像することができるが、ビタミンＥポリエチレングリコールスクシネート（ビタミンＥ　ＴＰＧＳ）である。

【００５１】

いくつかの実施形態において、１以上のアルコールは、エタノール、プロピルアルコール、ブチルアルコール、ペンタノール、ベンジルアルコール、それらの任意の異性体、又はそれらの任意の組合せから成る群から選択される。いくつかの実施形態において、１以上のグリコールは、エチレングリコール、プロピレングリコール、ブチレングリコール、ペンチレングリコール、それらの任意の異性体、及びそれらの任意の組合せから成る群から選択される。いくつかの実施形態において、１以上のグリコールは、ポリエチレングリコールなどのグリコール重合体を特に除外する。いくつかの実施形態において、１以上のグリコールは、２００ｇ／ｍｏｌより大きい分子量を有するグリコール重合体を特に除外

する。

【００５２】

いくつかの実施形態において、ベンゾジアゼピン薬は担体系中に、約１ｍｇ／ｍＬから約６００ｍｇ／ｍＬまでの濃度で存在する。いくつかの実施形態において、ベンゾジアゼピン薬は担体系中に、約１０ｍｇ／ｍＬから約２５０ｍｇ／ｍＬまでの濃度で存在する。いくつかの実施形態において、ベンゾジアゼピン薬は担体系中に、約２０ｍｇ／ｍＬから約５０ｍｇ／ｍＬまでの濃度で存在する。

【００５３】

いくつかの実施形態において、担体系は、約４５％から約８５％（Ｗ／Ｗ）までの量の、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、あるいはそれらの任意の組合せを備える。いくつかの実施形態において、担体系は、約６０％から約７５％（Ｗ／Ｗ）までの量の、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、あるいはそれらの任意の組合せを備える。いくつかの実施形態において、担体系は、約７０％（Ｗ／Ｗ）の量の、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、あるいはそれらの任意の組合せを備える。いくつかの実施形態において、特にベンゾジアゼピン薬の粒子懸濁液を考慮する場合、組成物はトコフェロール、特にトコフェロールと共有結合的に連結する親水基を有する合成トコフェロールを含み得る。他の実施形態において、特にベンゾジアゼピン薬の溶液を考慮する場合、トコフェロールは実質的に又は完全にビタミンＥ　ＴＰＧＳがない。

【００５４】

いくつかの実施形態において、担体系は約１０％から約５５％（Ｗ／Ｗ）の量の、１以上のアルコール又はグリコール、あるいはそれらの任意の組合せを備える。いくつかの実施形態において、担体系は約２５％から約４０％（Ｗ／Ｗ）の量の、１以上のアルコール又はグリコール、あるいはそれらの任意の組合せを備える。いくつかの実施形態において、担体系は約３０％（Ｗ／Ｗ）の量の、１以上のアルコール又はグリコール、あるいはそれらの任意の組合せを備える。いくつかの実施形態において、担体系における１以上のアルコール又はグリコール、あるいはそれらの任意の組合せの量は、約１０％から約５５％まで、約１０％から約４０％まで、約１０％から約３５％まで、約１２％から約５５％まで、約１２％から約４０％まで、約１２％から約３５％まで、約１５％から約５５％まで、約１５％から約４０％まで、約１５％から約３５％まで、約１０％、約１２．５％、約１５％、約１７．５％、約２０％、約２２．５％、約２５％、約２７．５％、約３０％、約３２．５％、約３５％、約３７．５％、約４０％、約４２．５％、約４５％、約４７．５％、約５０％、約５２．５％、又は約５５％（Ｗ／Ｗ）の量で備える。

【００５５】

いくつかの実施形態において、組成物は、医薬品有効成分、賦活剤、賦形剤、及びｐＨを調節し、組成物を緩衝し、分解を防ぎ、そして外観、匂い、又は味を改善するために用いられる剤から成る群から選択される、少なくとも１つの付加的な成分を備える。

【００５６】

いくつかの実施形態において、組成物はベンゾジアゼピン薬、天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、及びアルコール又はグリコールに加えて、少なくとも一つの透過賦活剤を備える。いくつかの実施形態において、透過賦活剤はアルキルグリコシドである。いくつかの実施形態において、アルキルグリコシドは、任意の疎水性アルキルにつなぎ合わされる任意の糖を指し、このことは米国特許第５，６６１，１３０号に記されており、これは全体として参照することにより本明細書中に組み込まれる。疎水性アルキルは、任意の適切な長さであることができ、例えば、炭鎖長が約９から約２４の炭素、特に炭鎖長が約１０から約１４の炭素であり得る。疎水性アルキルは、分岐であり得、及び／又は部分的に又は全体的に不飽和であり得る。アルキルは例えばカルボニル基を介してサッカライドコアにつなぎ合わされ、それによってエステル基が形成され得る。適切なアルキルグリコシドは、無毒性であり、非イオン性であり、本明細書中に記載されるように鼻腔内にベンゾジアゼピン薬が投与されるとその吸収を増大させることが

できるという特徴を有する。本発明に係るアルキルに共有結合的につなぎ合され得る例示的な糖類は、グルコース、マルトース、マルトトリオース、マルトテトロース、スクロース、及びトレハロースを含む。使用され得る例示的なアルキルグリコシドは、オクチル－、ノニル－、デシル－、ウンデシル－、ドデシル、トリデシル、テトラデシル、ペンタデシル、オクタデシルα－又はβ－Ｄ－マルトシド、－グルコシド、又はスクロシドを含む。いくつかの実施形態において、好ましいグリコシドは、９、１０、１２、１４、１６、１８、又は２０炭素原子のアルキル鎖にグリコシド結合により連結される、マルトース、スクロース、又はグルコースを含む。存在する場合、組成物中のアルキルグリコシドの量は、鼻腔内経路により投与されるベンゾジアゼピン薬の吸収を高めるために十分な量である。いくつかの実施形態において、組成物中のアルキルグリコシドの量は、ベンゾジアゼピン薬の吸収を高めるために選択され、同時に鼻粘膜を著しく刺激しない。いくつかの実施形態において、組成物中のアルキルグリコシドの量は約０．０１％（Ｗ／Ｖ）から約１％（Ｗ／Ｖ）までの範囲内である。いくつかの実施形態において、組成物中のアルキルグリコシドの量は約０．０５％（Ｗ／Ｖ）から約０．５％（Ｗ／Ｖ）まで、又は約０．１２５％（Ｗ／Ｖ）から約０．５％（Ｗ／Ｖ）までの範囲内である。

【００５７】

いくつかの実施形態において、組成物は薬学的に許容可能なスプレー製剤中にあり、さらに、１以上の、患者の鼻粘膜に組成物を投与することを備える。いくつかの実施形態において、治療的に効果的な量は約１ｍｇから約２０ｍｇまでのベンゾジアゼピンである。いくつかの実施形態において、医薬組成物は約１０μＬから約２００μＬまでの容量を有する、薬学的に許容可能なスプレー製剤中にある。

【００５８】

いくつかの実施形態において、組成物の投与は、組成物の治療的に効果的な量の少なくとも一部を、少なくとも１つの鼻孔の中へ噴霧する工程を備える。いくつかの実施形態において、組成物の投与は、組成物の治療的に効果的な量の少なくとも一部を、それぞれの鼻孔の中へ噴霧する工程を備える。いくつかの実施形態において、組成物の投与は、第１の量の組成物を第１の鼻孔の中へ噴霧する工程と、第２の量の組成物を第２の鼻孔の中へ噴霧する工程と、任意に事前に選択した時間遅延の後、第３の量の組成物を第１の鼻孔の中へ噴霧する工程とを備える。いくつかの実施形態は、任意に事前に選択した時間遅延の後、少なくとも第４の量の組成物を第２の鼻孔の中へ投与する工程を更に備える。

【００５９】

いくつかの実施形態において、組成物の投与は、組成物を用いて処置可能であり得る疾患の症状の発病前又は発病後の任意の時点で開始する。

【００６０】

定義

本明細書中に用いられるように、語句「治療的に効果的な量（又はより単純に「効果的な量」）」は、特定の治療応答を提供するのに十分な量を含み、この特定の治療応答を得るために、特定の処置を必要とする患者に薬が投与される。一般的な技術を有する臨床医は、薬の治療的に効果的な量は、患者、指示、及び投与される特定の薬に左右されることを認めるであろう。

【００６１】

本明細書中に用いられるように、修飾語句「約」は、その正式に認識された、おおよそという意味を有するよう意図されている。いくつかの実施形態において、用語は、修飾される値の特定の百分率内を意味するよう、より正確に解釈され得る。例えば、「約」はいくつかの実施形態において、±２０％、±１０％、±５％、±２％、又は±１％、又はそれ未満を意味し得る。

【００６２】

本明細書中に用いられるように、語句「アナログ又は誘導体」は、１又はそれより多い原子又は官能基が、異なる原子又は官能基と置換されているため、もう１つ別の分子とは異なる分子を含む。これにより同様の化学式を有するが異なる化学的及び／又は生物学的

特性を有する分子がもたらされ得る。

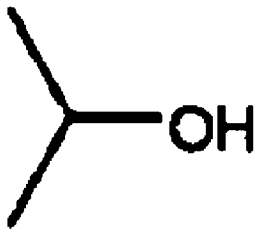
【００６３】

本明細書中に用いられるように、用語「異性体」は、同一の化学式を有する分子を含むが、それらの間で分子の配置は異なり得る。これらの異なる配置により、同一の化学式を有するが、異なる化学的特性を有する分子がもたらされ得る。制約のない例として、プロパノールは化学式C_3H_7OHを有する。それはプロパン－１－オールとして見出され得るが、その場合、－ＯＨは末端炭素に付着して見出される。代替的に、それはプロパン－２－オールとして見出され得るが、その場合－ＯＨは第２炭素に付着して見出される。

【００６４】

【化１】

プロパン-1-オール



プロパン-2-オール

【００６５】

本明細書中に用いられるように、用語「発作」は、一般に認められる型の発作を含み、欠神発作、ミオクローヌス発作、間代発作、強直性発作、強直間代発作、及び脱力発作を含む。しばしば発作、特に重症な強直性発作又は強直間代発作は、患者又は患者をよく知る人によく知られた、１以上の前兆により予測される。それぞれの患者は一般的に異なる型の前兆を経験する。それらは患者に特有のものである。しかしながら、前兆は、可聴の、視覚の、嗅覚の、又は触覚の感覚として分類され得、通常、又は少なくともしばしば患者が発作を経験することより先に起こる。（発作を患う全ての患者が前兆を経験するわけではない。しかしながら前兆は最悪の型の発作、特に強直間代発作を患う人の間では珍しいものではない。）

【００６６】

本明細書中に用いられるように、用語「予防」は、疾患の発病を未然に防ぐことを指し、一時的に未然に防ぐことを含む。発作の場合には、警戒前兆（ｗａｒｎｉｎｇ　ａｕｒａ）の恩恵を受け、又は受けずに、のいずれかで起こり得る。

【００６７】

本明細書中に用いられるように、用語「処置」は、疾患の強さ及び／又は持続時間を減じること、又は同様の効果を指す。用語はまた、このような「処置」の副作用をも包含する。

【００６８】

本明細書中に用いられるように、別段に制限された場合を除き、用語「一つの（ａ）」又は「一つの（ａｎ）」は１またはそれより多くを意味し得る。

【００６９】

本明細書中に用いられるように、用語「備える（ｃｏｍｐｒｉｓｉｎｇ）」は、その全ての変形において、請求項において用いられる移行句であり、本発明が、特に列挙された請求項要素を含む、又は含有するがそれらに限定されないということを示す。

【００７０】

本明細書中に用いられるように、用語「必須のものとして構成される」は、請求項において用いられる移行句であり、次に続く成分、部分、又は処理工程の一覧が、主張される組成物、機械、又は工程に存在せねばならないが、この請求項は、本発明の基礎的及び新

規の特性に実質的に影響を及ぼさない、一覧に記載されていない成分、部分、又は処理工程を受け入れる。

【００７１】

本明細書中に用いられるように、用語「構成される」は、請求項において用いられる移行句であり、主張される発明が請求項において説明されるそれらの要素のみを含むことを示す。

【００７２】

ベンゾジアゼピン薬

本発明の文脈において、用語「ベンゾジアゼピン薬」は、任意の治療上効果的なベンゾジアゼピン化合物、又は薬学的に許容可能な塩、又はそれらの組合せを含む。いくつかの実施形態において、ベンゾジアゼピンは　アルプラゾラム、ジアゼパム、フルラゼパム、ロラゼパム、メダゼパム、メキサゾラム、ミダゾラム、テマゼパム及び薬学的に許容可能な塩、及びそれらの組合せから成る群の部材を備える。

【００７３】

付加的なベンゾジアゼピン化合物は、低いバイオアベイラビリティ、乏しい薬物動態学的特性、又は乏しい薬力学的特性のいずれかのため、わずかな治療上の恩恵を有する、又はほとんど治療的な恩恵を有さないとこれまで見なされてきたが、以下を提供することができる、本発明を介した利用を見出し得るということは、当該分野の当業者によって認識されるべきである。それらは、ベンゾジアゼピン薬の改善されたバイオアベイラビリティ、経鼻経路を介するより高濃度のベンゾジアゼピン薬の送達、血漿中のベンゾジアゼピンの治療レベルのより速い達成、肝門脈（ｌｉｖｅｒ　ｐｏｒｔａｌ　ｖｅｉｎ）の回避、及び、付随する初回通過効果の回避、及び／又は、ベンゾジアゼピン薬の脳へのより速い提示である。

【００７４】

例えば、大抵のベンゾジアゼピンはごくわずかに水に溶けるにすぎないため、治療的に効果的な量は、粘膜への塗布に適した水性溶媒の容量には溶解されることができない。いくつかの実施形態においてベンゾジアゼピン薬を溶解する改善された能力を提供する、本担体系を用いることにより、本発明は、ベンゾジアゼピン薬が、鼻粘膜を含む１以上の粘膜に投与されることを可能にする。これにより、入院又は不要な不快感なく、薬を投与することが可能となる。その上、経鼻投与などの、本発明のいくつかの実施形態において、消化器系は大部分は迂回され得る。この後者の改善により、改善されたバイオアベイラビリティ、血漿中のベンゾジアゼピンの治療レベルのより速い達成、肝門脈（ｌｉｖｅｒ　ｐｏｒｔａｌ　ｖｅｉｎ）の回避、及び／又は、付随する初回通過効果の回避を生じさせることができる。

【００７５】

組成物の経鼻投与により、膜と脳の近い近接性のため、１以上のベンゾジアゼピン薬のより速い脳への提示がもたらされることができる。例えば、発病している患者は、硬直した筋肉及び制御できない動きに苦しむ。これが経口及び／又は静脈内投与を困難又は不便にし得る。しかしながら、経鼻通路は開いたままであり、容易に利用可能であり、従って本発明の有用な投与経路である。

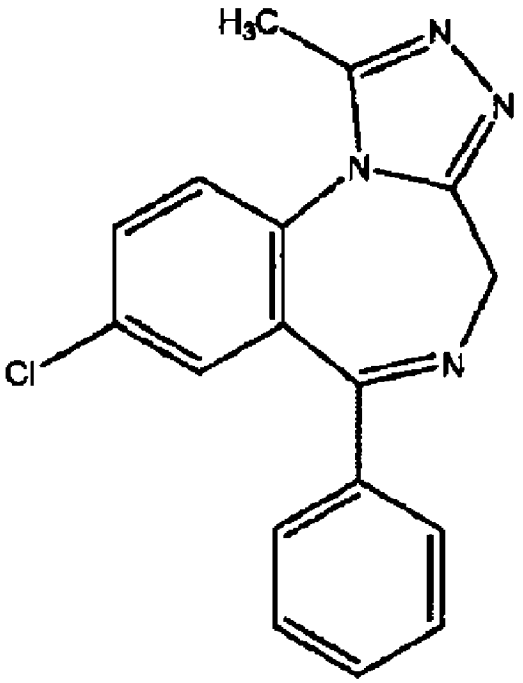
【００７６】

いくつかの実施形態において医薬組成物は、１以上の効果的な量のベンゾジアゼピン薬を用いた処置又は予防を受け入れる疾患に苦しむ患者を処置するために用いられる。制約のない例としてはこのような疾患は、不眠症、不安症、発作、筋痙攣及び硬直、並びに退薬症状を含むことができる。

【００７７】

いくつかの実施形態において、１以上のベンゾジアゼピン薬は、発作を処置し、発作から保護し、発作の強さを減じ又は改善し、発作の頻度を減じ又は改善し、及び／又は、発作の発生又は再発を予防するため、単独で又はもう一つの抗痙攣薬と併用して用いられる。

【００７８】
アルプラゾラム（８－クロロ－６－フェニル－１－メチル－４Ｈ－１，２，４－トリアゾロ［４，３－ａ］［１，４］ベンゾジアゼピン）
【００７９】
【化２】



【００８０】
アルプラゾラムは、鎮静の、精神安定の、及び筋弛緩性の特性を有するベンゾジアゼピン薬である。これは抗不安薬として分類される。アルプラゾラムは、パニック障害の処置に有用であるとも示されている。アルプラゾラムの投薬量は、指示により異なるが、治療量は投与量あたり約０．５から約４まで、好ましくは約１から約２ｍｇまでの範囲内で、１日あたり１から８、好ましくは２から８、いくつかの好ましい実施形態においては約４から約６回の範囲内であることが予期される。アルプラゾラムは、米国特許第３，９８７，０５２号に開示される工程を用いて製造され、これは全体として参照することにより本明細書中に組み込まれる。
【００８１】
いくつかの実施形態において、アルプラゾラムは、抗不安効果、鎮静効果、骨格筋弛緩効果、健忘作用、又は前述の効果の組合せを提供するため、単独で、又は他の薬と併用して用いられる。
【００８２】
いくつかの実施形態において、アルプラゾラムは、発作を処置し、発作から保護し、発作の強さを減じ又は改善し、発作の頻度を減じ又は改善し、及び／又は、発作の発生又は再発を予防するため、単独で又はもう一つの抗痙攣薬と併用して用いられる。発作から保護するため、患者が発病していない状態にある間、アルプラゾラムは、患者又は別の人（ヘルスケア専門家など）により投与され得る。発作からの保護が完全でない場合でさえ、アルプラゾラムの投与は、発作の強さを減じ又は改善し、及び／又は、発作の頻度を減じ又は改善し得る。いくつかの実施形態において、アルプラゾラムの投与は、発作の発生を予防し得る。いくつかの実施形態において、特に患者が連続的な発作又はてんかん重積状態を経験する傾向がある場合、アルプラゾラムの投与は、発作の循環を中断することを助け、従って発作の再発を予防し得る。ベンゾジアゼピン（ジアゼパムなど）に加えて、抗痙攣効果又は相乗的な抗痙攣効果を提供するため、他の抗痙攣薬がアルプラゾラムと組み

合わせられ得る。

【００８３】

アルプラゾラムはまた、患者が発作の状態にある間、もう一人の人（例えば、知人又は友人、家族の一員又はヘルスケア専門家）によって患者に投与されることもあり得る。従って、本発明によると、製剤の利点の一つは、急な治療環境において発作罹病者を処置するために、例えば経鼻的に、それらを投与され得ることである。ベンゾジアゼピン抗痙攣薬を、例えば経鼻投薬など、急に投薬することにより分け与えられ得る有益な治療効果の中には、発作の重症度の減少（例えば、筋肉の全身におよぶ弛緩、患者が経験する、発作に引き起こされた不安の減少、及び患者に幸福感を一般的に分け与えること）、発作の持続時間の減少、患者が反復発作を経験するであろう確率の減少、現在の発作と次の発作の間の間隔の拡大がある。従って、本発明のアルプラゾラム製剤、及び特に経鼻製剤は、いくつかの例においては約３０分未満、約１５分未満、約１０分未満、そしていくつかの場合においては約５分未満での、速やかな治療的な恩恵の発現を提供する。本発明のアルプラゾラム製剤、及び特に経鼻製剤は、静脈内の薬の投与や、直腸の薬の投与を必要としない、患者に治療上有益な薬を便利に投与することをもまた提供する。

【００８４】

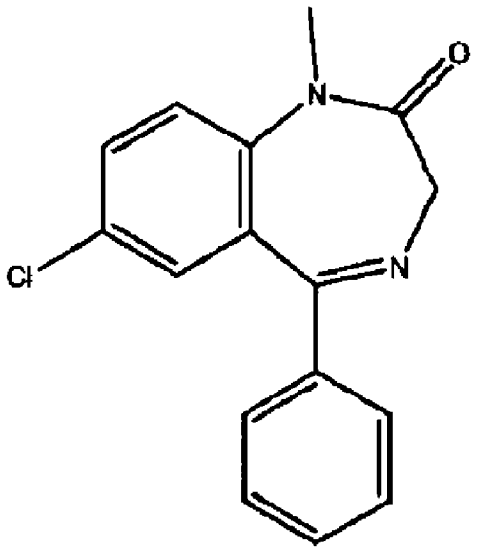
しばしば発作、特に重症な強直性発作又は強直間代発作は、患者又は患者をよく知る人によく知られた、１以上の前兆事象により予測される。これらの前兆はそれぞれの患者にほとんど独特であるが、可聴の、視覚の、嗅覚の、又は触覚の感覚として分類され得、通常、又は典型的に患者が発作を経験することより先に起こる。本発明のいくつかの実施形態において、方法は前兆の間に本発明に従ってベンゾジアゼピン薬の調製物を迅速に投与することを含む。いくつかの実施形態において、ベンゾジアゼピン薬のこのような耳内への（ｉｎｔｒａ－ａｕｒａｌ）投与、例えば経鼻投与による投与は、切迫した発作の効果（強さ、持続時間、又は両方）を予防又は少なくとも改善する。従って、本発明の文脈において、発作の予防は、警戒前兆（ｗａｒｎｉｎｇ　ａｕｒａ）の恩恵を受け、又は受けずに、のいずれかで、発作の発病を一時的に未然に防ぐことを指す。

【００８５】

ジアゼパム（７－クロロ－１－メチル－５－フェニル－１，３－ジヒドロ－２Ｈ－１，４－ベンゾジアゼピン－２－オン）

【００８６】

【化３】



【００８７】

ジアゼパムは、鎮静の、精神安定の、及び筋弛緩性の特性を有するベンゾジアゼピン薬である。これは抗不安薬、及び骨格筋弛緩薬として分類される。これは、抗不安の、抗痙

攣性の、鎮静の、骨格筋弛緩性の、及び健忘性の特性を有する。ジアゼパムの投薬量は、指示により異なり得るが、しかしながら、治療量は投与量あたり約１から約２０まで、好ましくは約２から約１０ｍｇまでの範囲内で、１日あたり１から８、好ましくは２から８、いくつかの好ましい実施形態においては約４から約６回の範囲内であることが予期される。ジアゼパムは、米国特許第３，３７１，０８５号、第３，１０９，８４３号、第３，１３６，８１５号、又は第３，１０２，１１６号の１つに開示される工程を用いて製造され、これらのそれぞれは全体として参照することにより本明細書中に組み込まれる。

【００８８】

いくつかの実施形態において、ジアゼパムは、抗不安効果、抗痙攣効果、鎮静効果、骨格筋弛緩効果、健忘作用、又は前述の効果の組合せを提供するため、単独で、又は他の薬と併用して用いられる。

【００８９】

いくつかの実施形態において、ジアゼパムは、発作を処置し、発作から保護し、発作の強さを減じ又は改善し、発作の頻度を減じ又は改善し、及び／又は、発作の発生又は再発を予防するため、単独で又はもう一つの抗痙攣薬と併用して用いられる。発作から保護するため、患者が発病していない状態にある間、ジアゼパムは、患者又は別の人（ヘルスケア専門家など）により投与され得る。発作からの保護が完全でない場合でさえ、ジアゼパムの投与は、発作の強さを減じ又は改善し、及び／又は、発作の頻度を減じ又は改善し得る。いくつかの実施形態において、ジアゼパムの投与は、発作の発生を予防し得る。いくつかの実施形態において、特に患者が連続的な発作又はてんかん重積状態を経験する傾向がある場合、ジアゼパムの投与は、発作の循環を中断することを助け、従って発作の再発を予防し得る。ベンゾジアゼピン（ジアゼパムなど）に加えて、相乗的な抗痙攣効果を提供するため、他の抗痙攣薬がジアゼパムと組み合わせられ得る。

【００９０】

ジアゼパムはまた、患者が発作の状態にある間、もう１人の人（例えば、知人又は友人、家族の一員又はヘルスケア専門家）によって患者に投与されることもあり得る。従って、本発明によると、製剤の利点の一つは、急な治療環境において発作罹病者を処置するために、例えば経鼻的に、それらを投与され得ることである。ベンゾジアゼピン抗痙攣薬を、例えば経鼻投薬など、急に投薬することにより分け与えられ得る有益な治療効果の中には、発作の重症度の減少（例えば、筋肉の全身におよぶ弛緩、患者が経験する、発作に引き起こされた不安の減少、及び患者に幸福感を一般的に分け与えること）、発作の持続時間の減少、患者が反復発作を経験するであろう確率の減少、現在の発作と次の発作の間の間隔の拡大がある。従って、本発明のジアゼパム製剤、及び特に経鼻製剤は、いくつかの例においては約３０分未満、約１５分未満、約１０分未満、そしていくつかの場合においては約５分未満での、速やかな治療的な恩恵の発現を提供する。本発明のジアゼパム製剤、及び特に経鼻製剤は、静脈内の薬の投与や、直腸の薬の投与を必要としない、患者への治療上有益な薬の便利な投与をもまた提供する。

【００９１】

しばしば発作、特に重症な強直性発作又は強直間代発作は、患者又は患者をよく知る人によく知られた、１以上の前兆事象により予測される。これらの前兆はそれぞれの患者にほとんど独特であるが、可聴の、視覚の、嗅覚の、又は触覚の感覚として分類され得、通常、又は典型的に患者が発作を経験することより先に起こる。本発明のいくつかの実施形態において、方法は前兆の間に本発明に従ってベンゾジアゼピン薬の調製物を迅速に投与することを含む。いくつかの実施形態において、ベンゾジアゼピン薬のこのような耳内への（ｉｎｔｒａ－ａｕｒａｌ）投与、例えば経鼻投与による投与は、切迫した発作の効果（強さ、持続時間、又は両方）を予防又は少なくとも改善する。従って、本発明の文脈において、発作の予防は、警戒前兆（ｗａｒｎｉｎｇ　ａｕｒａ）の恩恵を受け、又は受けずに、のいずれかで、発作の発病を一時的に未然に防ぐことを指す。

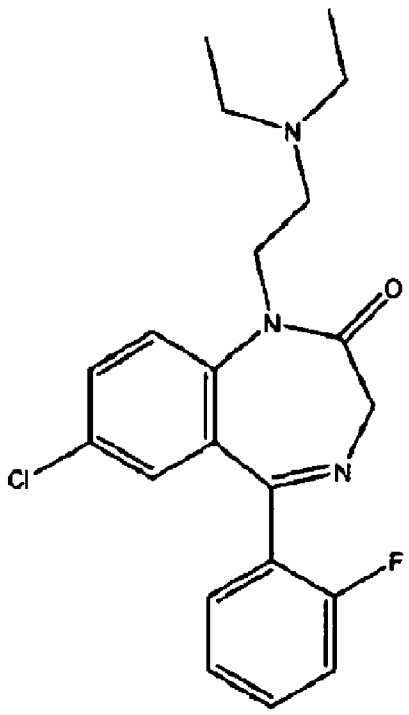
【００９２】

フルラゼパム（７－クロロ－５－（２－フルロフェニル）－２，３－ジヒドロ－１－（

２－（ジエチルアミノ）エチル）－１Ｈ－１，４－ベンゾジアゼピン－２－オン）

【００９３】

【化４】



【００９４】

フルラゼパムは、鎮静の（特に、催眠性の、及び催眠状態の）、抗不安の、抗痙攣性の、及び筋弛緩性の特性を有するベンゾジアゼピン薬である。これは鎮静薬、睡眠薬として分類される。フルラゼパムは、不眠症の処置に有用であると示されてきた。フルラゼパムの投薬量は、指示により異なるが、治療量は投与量あたり約５から約４０まで、好ましくは約２０から約３５ｍｇまでの範囲内で、１日あたり１から８、好ましくは２から８、いくつかの好ましい実施形態においては約４から約６回の範囲内であることが予期される。フルラゼパムは、米国特許第３，５６７，７１０号、又は第３，２９９，０５３号に開示される工程を用いて製造され、これらのそれぞれは全体として参照することにより本明細書中に組み込まれる。

【００９５】

いくつかの実施形態において、フルラゼパムは、抗不安効果、抗痙攣効果、鎮静効果、骨格筋弛緩効果、健忘作用、又は前述の効果の組合せを提供するため、単独で、又は他の薬と併用して用いられる。

【００９６】

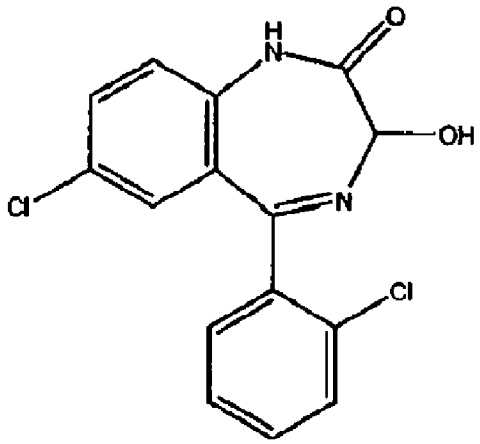
いくつかの実施形態において、フルラゼパムは、発作を処置し、発作から保護し、発作の強さを減じ又は改善し、発作の頻度を減じ又は改善し、及び／又は、発作の発生又は再発を予防するため、単独で又はもう一つの抗痙攣薬と併用して用いられる。発作から保護するため、患者が発病していない状態にある間、フルラゼパムは、患者又は別の人（ヘルスケア専門家など）により投与され得る。発作からの保護が完全でない場合でさえ、フルラゼパムの投与は、発作の強さを減じ又は改善し、及び／又は、発作の頻度を減じ又は改善し得る。いくつかの実施形態において、フルラゼパムの投与は、発作の発生を予防し得る。いくつかの実施形態において、特に患者が連続的な発作又はてんかん重積状態を経験する傾向がある場合、フルラゼパムの投与は、発作の循環を中断することを助け、従って発作の再発を予防し得る。ベンゾジアゼピン（ジアゼパムなど）に加えて、相乗的な抗痙攣効果を提供するため、他の抗痙攣薬がフルラゼパムと組み合わせられ得る。

【００９７】
フルラゼパムはまた、患者が発作の状態にある間、もう一人の人（例えば、知人又は友人、家族の一員又はヘルスケア専門家）によって患者に投与されることもあり得る。従って、本発明によると、製剤の利点の一つは、急な治療環境において発作罹病者を処置するために、例えば経鼻的に、それらを投与され得ることである。ベンゾジアゼピン抗痙攣薬を、例えば経鼻投薬など、急に投薬することにより分け与えられ得る有益な治療効果の中には、発作の重症度の減少（例えば、筋肉の全身におよぶ弛緩、患者が経験する、発作に引き起こされた不安の減少、及び患者に幸福感を一般的に分け与えること）、発作の持続時間の減少、患者が反復発作を経験するであろう確率の減少、現在の発作と次の発作の間の間隔の拡大がある。従って、本発明のフルラゼパム製剤、及び特に経鼻製剤は、いくつかの例においては約３０分未満、約１５分未満、約１０分未満、そしていくつかの場合においては約５分未満での、速やかな治療的な恩恵の発現を提供する。本発明のフルラゼパム製剤、及び特に経鼻製剤は、静脈内の薬の投与や、直腸の薬の投与を必要としない、患者への治療上有益な薬の便利な投与をもまた提供する。

【００９８】
しばしば発作、特に重症な強直性発作又は強直間代発作は、患者又は患者をよく知る人によく知られた、１以上の前兆事象により予測される。これらの前兆はそれぞれの患者にほとんど独特であるが、可聴の、視覚の、嗅覚の、又は触覚の感覚として分類され得、通常、又は典型的に患者が発作を経験することより先に起こる。本発明のいくつかの実施形態において、方法は前兆の間に本発明に従ってベンゾジアゼピン薬の調製物を迅速に投与することを含む。いくつかの実施形態において、ベンゾジアゼピン薬のこのような耳内への（ｉｎｔｒａ－ａｕｒａｌ）投与、例えば経鼻投与による投与は、切迫した発作の効果（強さ、持続時間、又は両方）を予防又は少なくとも改善する。従って、本発明の文脈において、発作の予防は、警戒前兆（ｗａｒｎｉｎｇ　ａｕｒａ）の恩恵を受け、又は受けずに、のいずれかで、発作の発病を一時的に未然に防ぐことを指す。

【００９９】
ロラゼパム（７－クロロ－５－（２－クロロフェニル）－３－ヒドロキシ－１，３－ジヒドロ－２Ｈ－１，４－ベンゾジアゼピン－２－オン）

【０１００】
【化５】



【０１０１】
ロラゼパムは、鎮静の、精神安定の、抗痙攣性の、健忘性の、及び筋弛緩性の特性を有するベンゾジアゼピン薬である。これは抗不安薬として分類される。ロラゼパムはまた、吐き気の処置に有用であると示されてきた。ロラゼパムの投薬量は、指示により異なるが、治療量は投与量あたり約０．１から約１０まで、好ましくは約０．２から約１ｍｇまで

の範囲内で、１日あたり１から８、好ましくは２から８、いくつかの好ましい実施形態においては約４から約６回の範囲内であることが予期される。ロラゼパムは、米国特許第３，２９６，２４９号に開示される工程を用いて製造され、これは全体として参照することにより本明細書中に組み込まれる。

【０１０２】

いくつかの実施形態において、ロラゼパムは、抗不安効果、抗痙攣効果、鎮静効果、骨格筋弛緩効果、健忘作用、又は前述の効果の組合せを提供するため、単独で、又は他の薬と併用して用いられる。

【０１０３】

いくつかの実施形態において、ロラゼパムは、発作を処置し、発作から保護し、発作の強さを減じ又は改善し、発作の頻度を減じ又は改善し、及び／又は、発作の発生又は再発を予防するため、単独で又はもう一つの抗痙攣薬と併用して用いられる。発作から保護するため、患者が発病していない状態にある間、ロラゼパムは、患者又は別の人（ヘルスケア専門家など）により投与され得る。発作からの保護が完全でない場合でさえ、ロラゼパムの投与は、発作の強さを減じ又は改善し、及び／又は、発作の頻度を減じ又は改善し得る。いくつかの実施形態において、ロラゼパムの投与は、発作の発生を予防し得る。いくつかの実施形態において、特に患者が連続的な発作又はてんかん重積状態を経験する傾向がある場合、ロラゼパムの投与は、発作の循環を中断することを助け、従って発作の再発を予防し得る。ベンゾジアゼピン（ジアゼパムなど）に加えて、相乗的な抗痙攣効果を提供するため、他の抗痙攣薬がロラゼパムと組み合わせられ得る。

【０１０４】

ロラゼパムはまた、患者が発作の状態にある間、もう一人の人（例えば、知人又は友人、家族の一員又はヘルスケア専門家）によって患者に投与されることもあり得る。従って、本発明によると、製剤の利点の一つは、急な治療環境において発作罹病者を処置するために、例えば経鼻的に、それらを投与され得ることである。ベンゾジアゼピン抗痙攣薬を、例えば経鼻投薬など、急に投薬することにより分け与えられ得る有益な治療効果の中には、発作の重症度の減少（例えば、筋肉の全身におよぶ弛緩、患者が経験する、発作に引き起こされた不安の減少、及び患者に幸福感を一般的に分け与えること）、発作の持続時間の減少、患者が反復発作を経験するであろう確率の減少、現在の発作と次の発作の間の間隔の拡大がある。従って、本発明のロラゼパム製剤、及び特に経鼻製剤は、いくつかの例においては約３０分未満、約１５分未満、約１０分未満、そしていくつかの場合においては約５分未満での、速やかな治療的な恩恵の発現を提供する。本発明のロラゼパム製剤、及び特に経鼻製剤は、静脈内の薬の投与や、直腸の薬の投与を必要としない、患者への治療上有益な薬の便利な投与をもまた提供する。

【０１０５】

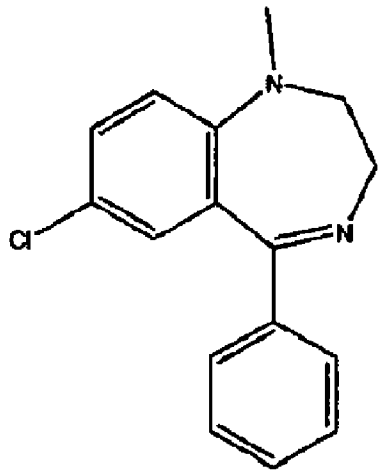
しばしば発作、特に重症な強直性発作又は強直間代発作は、患者又は患者をよく知る人によく知られた、１以上の前兆事象により予測される。これらの前兆はそれぞれの患者にほとんど独特であるが、可聴の、視覚の、嗅覚の、又は触覚の感覚として分類され得、通常、又は典型的に患者が発作を経験することより先に起こる。本発明のいくつかの実施形態において、方法は前兆の間に本発明に従ってベンゾジアゼピン薬の調製物を迅速に投与することを含む。いくつかの実施形態において、ベンゾジアゼピン薬のこのような耳内への（ｉｎｔｒａ－ａｕｒａｌ）投与、例えば経鼻投与による投与は、切迫した発作の効果（強さ、持続時間、又は両方）を予防又は少なくとも改善する。従って、本発明の文脈において、発作の予防は、警戒前兆（ｗａｒｎｉｎｇ　ａｕｒａ）の恩恵を受け、又は受けずに、のいずれかで、発作の発病を一時的に未然に防ぐことを指す。

【０１０６】

メダゼパム（７－クロロ－１－メチル－５－フェニル－２，３－ジヒドロ－１Ｈ－１，４－ベンゾジアゼピン）

【０１０７】

【化６】



【０１０８】
メダゼパムは、鎮静の、精神安定の、抗痙攣性の、健忘性の、及び筋弛緩性の特性を有するベンゾジアゼピン薬である。これは抗不安薬として分類される。メダゼパムはまた、吐き気の処置に有用であると示されてきた。メダゼパムの投薬量は、指示により異なるが、治療量は投与量あたり約０．１から約１０まで、好ましくは約０．２から約１ｍｇまでの範囲内で、１日あたり１から８、好ましくは２から８、いくつかの好ましい実施形態においては約４から約６回の範囲内であることが予期される。メダゼパムは、米国特許第３，２４３，４２７号に開示される工程を用いて製造され、これは全体として参照することにより本明細書中に組み込まれる。

【０１０９】
いくつかの実施形態において、メダゼパムは、抗不安効果、抗痙攣効果、鎮静効果、骨格筋弛緩効果、健忘作用、又は前述の効果の組合せを提供するため、単独で、又は他の薬と併用して用いられる。

【０１１０】
いくつかの実施形態において、メダゼパムは、発作を処置し、発作から保護し、発作の強さを減じ又は改善し、発作の頻度を減じ又は改善し、及び／又は、発作の発生又は再発を予防するため、単独で又はもう一つの抗痙攣薬と併用して用いられる。発作から保護するため、患者が発病していない状態にある間、メダゼパムは、患者又は別の人（ヘルスケア専門家など）により投与され得る。発作からの保護が完全でない場合でさえ、メダゼパムの投与は、発作の強さを減じ又は改善し、及び／又は、発作の頻度を減じ又は改善し得る。いくつかの実施形態において、メダゼパムの投与は、発作の発生を予防し得る。いくつかの実施形態において、特に患者が連続的な発作又はてんかん重積状態を経験する傾向がある場合、メダゼパムの投与は、発作の循環を中断することを助け、従って発作の再発を予防し得る。ベンゾジアゼピン（ジアゼパムなど）に加えて、相乗的な抗痙攣効果を提供するため、他の抗痙攣薬がメダゼパムと組み合わせられ得る。

【０１１１】
メダゼパムはまた、患者が発作の状態にある間、もう一人の人（例えば、知人又は友人、家族の一員又はヘルスケア専門家）によって患者に投与されることもあり得る。従って、本発明によると、製剤の利点の一つは、急な治療環境において発作罹病者を処置するために、例えば経鼻的に、それらを投与され得ることである。ベンゾジアゼピン抗痙攣薬を、例えば経鼻投薬など、急に投薬することにより分け与えられ得る有益な治療効果の中には、発作の重症度の減少（例えば、筋肉の全身におよぶ弛緩、患者が経験する、発作に引き起こされた不安の減少、及び患者に幸福感を一般的に分け与えること）、発作の持続時間の減少、患者が反復発作を経験するであろう確率の減少、現在の発作と次の発作の間の

間隔の拡大がある。従って、本発明のメダゼパム製剤、及び特に経鼻製剤は、いくつかの例においては約３０分未満、約１５分未満、約１０分未満、そしていくつかの場合においては約５分未満での、速やかな治療的な恩恵の発現を提供する。本発明のメダゼパム製剤、及び特に経鼻製剤は、静脈内の薬の投与や、直腸の薬の投与を必要としない、患者への治療上有益な薬の便利な投与をもまた提供する。

【０１１２】

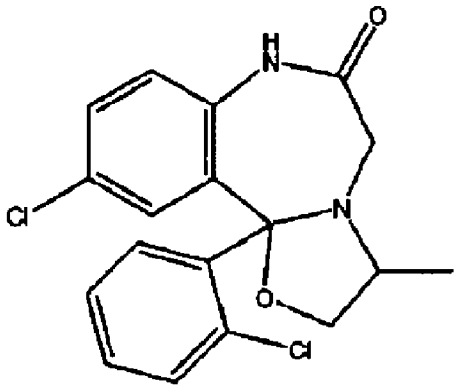
しばしば発作、特に重症な強直性発作又は強直間代発作は、患者又は患者をよく知る人によく知られた、１以上の前兆事象により予測される。これらの前兆はそれぞれの患者にほとんど独特であるが、可聴の、視覚の、嗅覚の、又は触覚の感覚として分類され得、通常、又は典型的に患者が発作を経験することより先に起こる。本発明のいくつかの実施形態において、方法は前兆の間に本発明に従ってベンゾジアゼピン薬の調製物を迅速に投与することを含む。いくつかの実施形態において、ベンゾジアゼピン薬のこのような耳内への（ｉｎｔｒａ－ａｕｒａｌ）投与、例えば経鼻投与による投与は、切迫した発作の効果（強さ、持続時間、又は両方）を予防又は少なくとも改善する。従って、本発明の文脈において、発作の予防は、警戒前兆（ｗａｒｎｉｎｇ　ａｕｒａ）の恩恵を受け、又は受けずに、のいずれかで、発作の発病を一時的に未然に防ぐことを指す。

【０１１３】

メキサゾラム（１０－クロロ－１１ｂ－（２－クロロフェニル）－１，３，７，１１ｂ－テトラヒドロ－３－メチルオキサゾロ［３，２－ｄ］［１，４］ベンゾジアゼピン－６（５Ｈ）－オン）

【０１１４】

【化７】



【０１１５】

メキサゾラムは、鎮静の、精神安定の、抗痙攣性の、健忘性の、及び筋弛緩性の特性を有するベンゾジアゼピン薬である。これは抗不安薬として分類される。メキサゾラムはまた、吐き気の処置に有用であると示されてきた。メキサゾラムの投薬量は、指示により異なるが、治療量は投与量あたり約０．１から約１０まで、好ましくは約０．２から約１ｍｇまでの範囲内で、１日あたり１から８、好ましくは２から８、いくつかの好ましい実施形態においては約４から約６回の範囲内であることが予期される。メキサゾラムは、米国特許第３，７２２，３７１号に開示される工程を用いて製造され、これは全体として参照することにより本明細書中に組み込まれる。

【０１１６】

いくつかの実施形態において、メキサゾラムは、抗不安効果、抗痙攣効果、鎮静効果、骨格筋弛緩効果、健忘作用、又は前述の効果の組合せを提供するため、単独で、又は他の薬と併用して用いられる。

【０１１７】

いくつかの実施形態において、メキサゾラムは、発作を処置し、発作から保護し、発作の強さを減じ又は改善し、発作の頻度を減じ又は改善し、及び／又は、発作の発生又は再

発を予防するため、単独で又はもう一つの抗痙攣薬と併用して用いられる。発作から保護するため、患者が発病していない状態にある間、メキサゾラムは、患者又は別の人（ヘルスケア専門家など）により投与され得る。発作からの保護が完全でない場合でさえ、メキサゾラムの投与は、発作の強さを減じ又は改善し、及び／又は、発作の頻度を減じ又は改善し得る。いくつかの実施形態において、メキサゾラムの投与は、発作の発生を予防し得る。いくつかの実施形態において、特に患者が連続的な発作又はてんかん重積状態を経験する傾向がある場合、メキサゾラムの投与は、発作の循環を中断することを助け、従って発作の再発を予防し得る。ベンゾジアゼピン（ジアゼパムなど）に加えて、相乗的な抗痙攣効果を提供するため、他の抗痙攣薬がメキサゾラムと組み合わせられ得る。

【０１１８】

メキサゾラムはまた、患者が発作の状態にある間、もう一人の人（例えば、知人又は友人、家族の一員又はヘルスケア専門家）によって患者に投与されることもあり得る。従って、本発明によると、製剤の利点の一つは、急な治療環境において発作罹病者を処置するために、例えば経鼻的に、それらを投与され得ることである。ベンゾジアゼピン抗痙攣薬を、例えば経鼻投薬など、急に投薬することにより分け与えられ得る有益な治療効果の中には、発作の重症度の減少（例えば、筋肉の全身におよぶ弛緩、患者が経験する、発作に引き起こされた不安の減少、及び患者に幸福感を一般的に分け与えること）、発作の持続時間の減少、患者が反復発作を経験するであろう確率の減少、現在の発作と次の発作の間の間隔の拡大がある。従って、本発明のメキサゾラム製剤、及び特に経鼻製剤は、いくつかの例においては約３０分未満、約１５分未満、約１０分未満、そしていくつかの場合においては約５分未満での、速やかな治療的な恩恵の発現を提供する。本発明のメキサゾラム製剤、及び特に経鼻製剤は、静脈内の薬の投与や、直腸の薬の投与を必要としない、患者への治療上有益な薬の便利な投与をもまた提供する。

【０１１９】

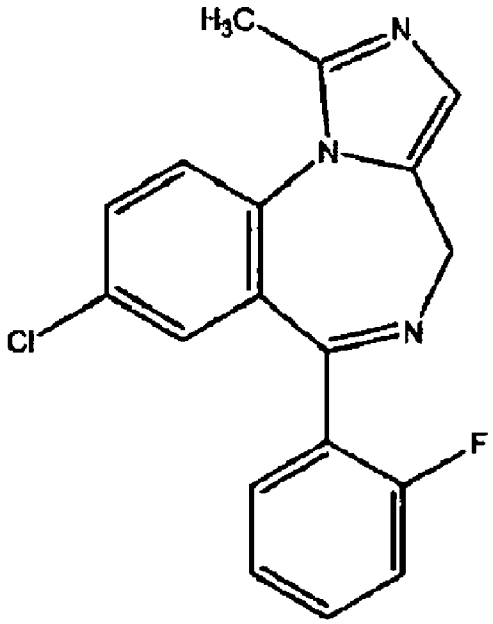
しばしば発作、特に重症な強直性発作又は強直間代発作は、患者又は患者をよく知る人によく知られた、１以上の前兆事象により予測される。これらの前兆はそれぞれの患者にほとんど独特であるが、可聴の、視覚の、嗅覚の、又は触覚の感覚として分類され得、通常、又は典型的に患者が発作を経験することより先に起こる。本発明のいくつかの実施形態において、方法は前兆の間に本発明に従ってベンゾジアゼピン薬の調製物を迅速に投与することを含む。いくつかの実施形態において、ベンゾジアゼピン薬のこのような耳内への（ｉｎｔｒａ－ａｕｒａｌ）投与、例えば経鼻投与による投与は、切迫した発作の効果（強さ、持続時間、又は両方）を予防又は少なくとも改善する。従って、本発明の文脈において、発作の予防は、警戒前兆（ｗａｒｎｉｎｇ　ａｕｒａ）の恩恵を受け、又は受けずに、のいずれかで、発作の発病を一時的に未然に防ぐことを指す。

【０１２０】

ミダゾラム（８－クロロ－６－（２－フルオロフェニル）－１－メチル－４Ｈ－イミダゾ（１，５－ａ）ベンゾジアゼピン）

【０１２１】

【化８】



【０１２２】

ミダゾラムは、抗不安の、健忘性の、催眠性の、抗痙攣性の、骨格筋弛緩性の、及び鎮静の特性を有する、三環系のベンゾジアゼピンである。ミダゾラムは、約４より低いｐＨで水に溶解できると見なされているが、中性ｐＨ（例えば、約６から８）で大抵の水溶液に比較的に不溶性である。従って、いくつかの実施形態において、ミダゾラムの水性の経鼻用調製物は、約５．５より上、好ましくは約６．０より上、又は約６．５より上のｐＨを有することが好ましい。いくつかの好ましい実施形態において、ｐＨは約６と９の間、約６と８の間である。脂溶性（およそ中性ｐＨで）のミダゾラムは、鼻粘膜中に急速に吸収され、ミダゾラムの能率的な摂取へ導くため、ミダゾラムの調製物は特に経鼻投与に適していると考えられる。更に、ミダゾラムは、ハイドロフルオロカーボン噴射剤、炭化水素噴射剤などといったエアロゾル投与技術において既知であるものなどの、非水性の送達ビヒクルの中に処方され得ると考えられる。

【０１２３】

ミダゾラムの投薬量は、指示により異なるが、治療量は投与量あたり約０．１から約２０まで、好ましくは約０．２から約１０ｍｇまでの範囲内で、１日あたり１から８、好ましくは２から８、いくつかの好ましい実施形態においては約４から約６回の範囲内であることが予期される。ミダゾラムは、米国特許第４，２８０，９５７号、又は第５，８３１，０８９号の一つに開示される工程を用いて製造され、これらのそれぞれは全体として参照することにより本明細書中に組み込まれる。

【０１２４】

いくつかの実施形態において、ミダゾラムは、抗不安効果、抗痙攣効果、鎮静効果、骨格筋弛緩効果、健忘作用、又は前述の効果の組合せを提供するため、単独で、又は他の薬と併用して用いられる。

【０１２５】

いくつかの実施形態において、ミダゾラムは、発作を処置し、発作から保護し、発作の強さを減じ又は改善し、発作の頻度を減じ又は改善し、及び／又は、発作の発生又は再発を予防するため、単独で又はもう一つの抗痙攣薬と併用して用いられる。発作から保護するため、患者が発病していない状態にある間、ミダゾラムは、患者又は別の人（ヘルスケア専門家など）により投与され得る。発作からの保護が完全でない場合でさえ、ミダゾラムの投与は、発作の強さを減じ又は改善し、及び／又は、発作の頻度を減じ又は改善し得

る。いくつかの実施形態において、ミダゾラムの投与は、発作の発生を予防し得る。いくつかの実施形態において、特に患者が連続的な発作又はてんかん重積状態を経験する傾向がある場合、ミダゾラムの投与は、発作の循環を中断することを助け、従って発作の再発を予防し得る。ベンゾジアゼピン（ジアゼパムなど）に加えて、相乗的な抗痙攣効果を提供するため、他の抗痙攣薬がミダゾラムと組み合わせられ得る。

【０１２６】

ミダゾラムはまた、患者が発作の状態にある間、もう一人の人（例えば、知人又は友人、家族の一員又はヘルスケア専門家）によって患者に投与されることもあり得る。従って、本発明によると、製剤の利点の一つは、急な治療環境において発作罹病者を処置するために、例えば経鼻的に、それらを投与され得ることである。ベンゾジアゼピン抗痙攣薬を、例えば経鼻投薬など、急に投薬することにより分け与えられ得る有益な治療効果の中には、発作の重症度の減少（例えば、筋肉の全身におよぶ弛緩、患者が経験する、発作に引き起こされた不安の減少、及び患者に幸福感を一般的に分け与えること）、発作の持続時間の減少、患者が反復発作を経験するであろう確率の減少、現在の発作と次の発作の間の間隔の拡大がある。従って、本発明のミダゾラム製剤、及び特に経鼻製剤は、いくつかの例においては約３０分未満、約１５分未満、約１０分未満、そしていくつかの場合においては約５分未満での、速やかな治療的な恩恵の発現を提供する。本発明のミダゾラム製剤、及び特に経鼻製剤は、静脈内の薬の投与や、直腸の薬の投与を必要としない、患者への治療上有益な薬の便利な投与をもまた提供する。

【０１２７】

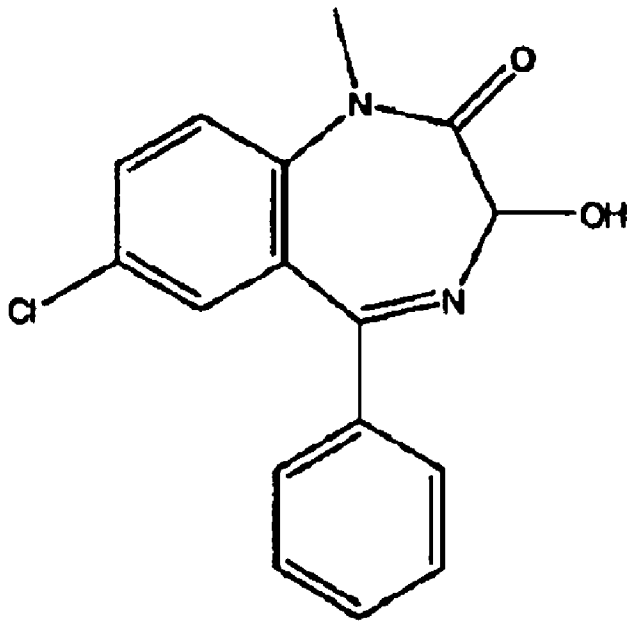
しばしば発作、特に重症な強直性発作又は強直間代発作は、患者又は患者をよく知る人によく知られた、１以上の前兆事象により予測される。これらの前兆はそれぞれの患者にほとんど独特であるが、可聴の、視覚の、嗅覚の、又は触覚の感覚として分類され得、通常、又は典型的に患者が発作を経験することより先に起こる。本発明のいくつかの実施形態において、方法は前兆の間に本発明に従ってベンゾジアゼピン薬の調製物を迅速に投与することを含む。いくつかの実施形態において、ベンゾジアゼピン薬のこのような耳内への（ｉｎｔｒａ－ａｕｒａｌ）投与、例えば経鼻投与による投与は、切迫した発作の効果（強さ、持続時間、又は両方）を予防又は少なくとも改善する。従って、本発明の文脈において、発作の予防は、警戒前兆（ｗａｒｎｉｎｇ　ａｕｒａ）の恩恵を受け、又は受けずに、のいずれかで、発作の発病を一時的に未然に防ぐことを指す。

【０１２８】

テマゼパム（７－クロロ－１－メチル－５－フェニル－３－ヒドロキシ－１，３－ジヒドロ－２Ｈ－１，４－ベンゾジアゼピン－２－オン）

【０１２９】

【化９】



【０１３０】

テマゼパムは、鎮静の、精神安定の、抗痙攣性の、健忘性の、及び筋弛緩性の特性を有するベンゾジアゼピン薬である。これは抗不安薬として分類される。テマゼパムはまた、吐き気の処置に有用であると示されてきた。テマゼパムの投薬量は、指示により異なるが、治療量は投与量あたり約１から約５０まで、好ましくは約５から約３０ｍｇまでの範囲内で、１日あたり１から８、好ましくは２から８、いくつかの好ましい実施形態においては約４から約６回の範囲内であることが予期される。テマゼパムは、米国特許第３，３４０，２５３号、又は第３，３７４，２２５号に開示される工程を用いて製造され得、これらのそれぞれは全体として参照することにより本明細書中に組み込まれる。

【０１３１】

いくつかの実施形態において、テマゼパムは、抗不安効果、抗痙攣効果、鎮静効果、骨格筋弛緩効果、健忘作用、又は前述の効果の組合せを提供するため、単独で、又は他の薬と併用して用いられる。

【０１３２】

いくつかの実施形態において、テマゼパムは、発作を処置し、発作から保護し、発作の強さを減じ又は改善し、発作の頻度を減じ又は改善し、及び／又は、発作の発生又は再発を予防するため、単独で又はもう一つの抗痙攣薬と併用して用いられる。発作から保護するため、患者が発病していない状態にある間、テマゼパムは、患者又は別の人（ヘルスケア専門家など）により投与され得る。発作からの保護が完全でない場合でさえ、テマゼパムの投与は、発作の強さを減じ又は改善し、及び／又は、発作の頻度を減じ又は改善し得る。いくつかの実施形態において、テマゼパムの投与は、発作の発生を予防し得る。いくつかの実施形態において、特に患者が連続的な発作又はてんかん重積状態を経験する傾向がある場合、テマゼパムの投与は、発作の循環を中断することを助け、従って発作の再発を予防し得る。ベンゾジアゼピン（ジアゼパムなど）に加えて、相乗的な抗痙攣効果を提供するため、他の抗痙攣薬がテマゼパムと組み合わせられ得る。

【０１３３】

テマゼパムはまた、患者が発作の状態にある間、もう一人の人（例えば、知人又は友人、家族の一員又はヘルスケア専門家）によって患者に投与されることもあり得る。従って、本発明によると、製剤の利点の一つは、急な治療環境において発作罹病者を処置するために、例えば経鼻的に、それらを投与され得ることである。ベンゾジアゼピン抗痙攣薬を

、例えば経鼻投薬など、急に投薬することにより分け与えられ得る有益な治療効果の中には、発作の重症度の減少（例えば、筋肉の全身におよぶ弛緩、患者が経験する、発作に引き起こされた不安の減少、及び患者に幸福感を一般的に分け与えること）、発作の持続時間の減少、患者が反復発作を経験するであろう確率の減少、現在の発作と次の発作の間の間隔の拡大がある。従って、本発明のテマゼパム製剤、及び特に経鼻製剤は、いくつかの例においては約３０分未満、約１５分未満、約１０分未満、そしていくつかの場合においては約５分未満での、速やかな治療的な恩恵の発現を提供する。本発明のテマゼパム製剤、及び特に経鼻製剤は、静脈内の薬の投与や、直腸の薬の投与を必要としない、患者への治療上有益な薬の便利な投与をもまた提供する。

【０１３４】

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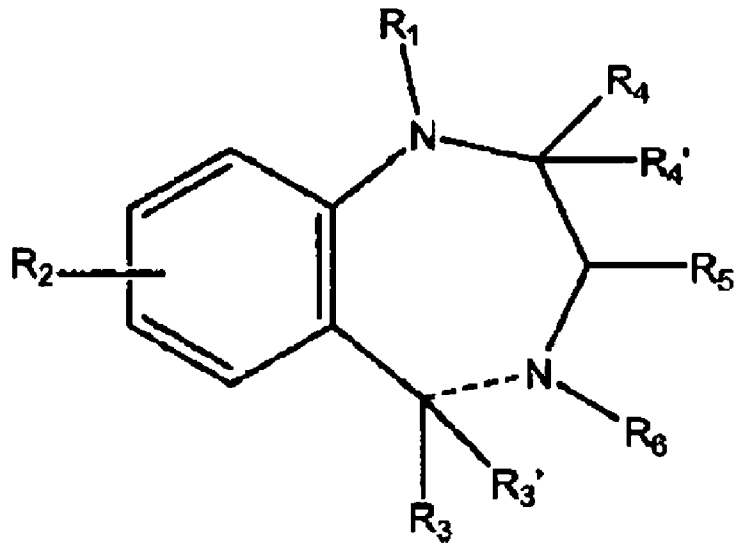
【０１３５】

薬学的に許容可能な塩

ベンゾジアゼピンは、概して式Ｉの塩基性構造を有する。

【０１３６】

【化１０】



式Ｉ

【０１３７】

ここでＲ１からＲ５は置換基である。特定の実施形態において、Ｒ１は任意に置換されたアルキルであるか、又はＲ４とともに環を形成し、Ｒ２はハロゲン（例えばＣｌ、Ｂｒ）であり、Ｒ３は任意に置換されたアリール（例えば、２－クロロ又は２－フルオロフェニル）であり、Ｒ５はＨ又はＯＨであり、Ｒ４及びＲ４’は共に、それらが付いている炭素とともにカルボニル（Ｃ＝Ｏ）を形成する、或いは、Ｒ４及びＲ１はそれらが各々付い

ているジアゼパム環原子とともに任意に置換された複素環式環を形成し、R_3'及びR_6はともに二重結合を形成する、又は、それらが各々付いているジアゼパム環原子とともに任意に置換された複素環式環を形成するよう結合され得る。このような塩基性化合物は、薬学的に許容可能な無機酸及び薬学的に許容可能な有機酸などの薬学的に許容可能な酸を用いて、酸付加塩を形成し得る。

【０１３８】

薬学的に許容可能な無機酸は、ＨＣｌ、H_2SO_4、H_2SO_3、H_3PO_4、H_3PO_3、及び当該分野の当業者に認められる他のものを含む。薬学的に許容可能な有機酸は、酢酸、安息香酸、酒石酸、クエン酸、シュウ酸、マレイン酸、マロン酸等を含む。従って、いくつかの実施形態において、薬学的に許容可能な酸は、１－ヒドロキシ－２－ナフトエ酸、２，２－ジクロロ酢酸、２－ヒドロキシエタンスルホン酸、２－オキソグルタル酸、４－アセトアミド安息香酸、４－アミノサリチル酸、酢酸、アジピン酸、アスコルビン酸（Ｌ）、アスパラギン酸（Ｌ）、ベンゼンスルホン酸、安息香酸、樟脳酸（＋）、カンファー－１０－スルホン酸（＋）、カプリン酸（デカン酸）、カプロン酸（ヘキサン酸）、カプリル酸（オクタン酸）、炭酸、桂皮酸、クエン酸、シクラミン酸、ドデシル硫酸、エタン－１，２－ジスルホン酸、エタンスルホン酸、ギ酸、フマル酸、ガラクタル酸、ゲンチシン酸、グルコヘプトン酸（Ｄ）、グルコン酸（Ｄ）、グルクロン酸（Ｄ）、グルタミン酸、グルタル酸、グリセロリン酸、グリコール酸、馬尿酸、臭化水素酸、塩酸、イソ酪酸、乳酸（ＤＬ）、ラクトビオン酸、ラウリン酸、マレイン酸、リンゴ酸（－Ｌ）、マロン酸、マンデル酸（ＤＬ）、メタンスルホン酸、ベンゼンスルホン酸（ベシル酸）、ナフタレン－１，５－ジスルホン酸、ナフタレン－２－スルホン酸、ニコチン酸、硝酸、オレイン酸、シュウ酸、パルミチン酸、パモン酸（ｐａｍｏｉｃ　ａｃｉｄ）、リン酸、プロピオン酸、ピログルタミン酸（－Ｌ）、サリチル酸、セバシン酸、ステアリン酸、コハク酸、硫酸、酒石酸（＋Ｌ）、チオシアン酸、トルエンスルホン酸（ｐ）及びウンデシレン酸から構成される群から選択され得る。他の薬学的に許容可能な酸は、薬学的に許容可能な酸性（アニオン性）ポリマー、又は薬学的に許容可能な両性ポリマーであり得る。当該分野の当業者は、酸付加塩を作り出すため、他の塩基性の医薬品有効成分が前述の酸と結合され得ることを認める。同様に、当該分野の当業者は、いくつかの実施形態において、いくつか又は全ての加えられた酸がそれ自体で医薬品有効成分となることが好都合であることを認める。

【０１３９】

いくつかの実施形態において、本発明は、１以上の酸性の医薬品有効成分を備える経鼻組成物を提供する。上記の化合物のいずれが酸性であるかを決定することは、当該技術分野の当業者において、十分に考慮されている。このような化合物は、例えば、１以上の無機塩基（例えばＮａＯＨ、ＫＯＨ、$NaHCO_3$、Na_2CO_3、NH_3）、又は有機塩基を加えることにより、塩基付加塩として調製され得る。薬学的に許容化可能な塩基を選ぶことは当該分野の当業者において考慮されている。

【０１４０】

既知のベンゾジアゼピン化合物は、抗不安の、抗痙攣の、鎮静の、及び／又は骨格筋弛緩性の効果を有する。用語「抗痙攣の」は、発作を処置すること、発作から保護すること、発作の強さを減じ又は改善すること、発作の頻度を減じ又は改善すること、及び／又は、発作の発生又は再発を予防することを含む。この点において、発作を処置することは、進行中の発作の休止、進行中の発作の強さの減少、進行中の発作の持続時間の減少を含む。発作から保護することは、接近する発作を未然に防ぐことを含む。

【０１４１】

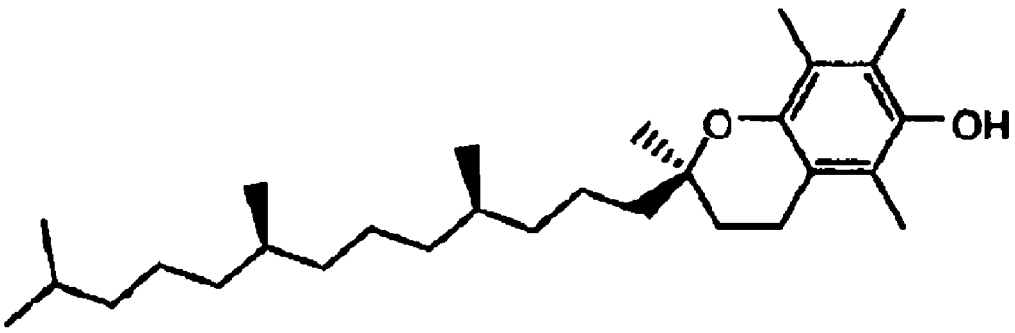
担体系

ビタミンＥは、脂溶性のメチル化されたフェノールである。この分類を備える少なくとも８つの天然由来の化合物が存在し、それらは、α－トコフェロール、β－トコフェロール、γ－トコフェロール、δ－トコフェロール、α－トコトリエノール、β－トコトリエノール、γ－トコトリエノール、及びδ－トコトリエノールで、これらの全ては本発明の

組成物及び方法において用いられ得る。これらの化合物のそれぞれに多数の異性体が存在し、それらの全ては本発明の組成物及び方法において用いられ得る。これらの化合物のそれぞれにまた、トコフェルソランを含む、多数のエステルが存在し、それらのすべては本発明の組成物及び方法において用いられ得る。本明細書中に用いられるように、ビタミンＥは、任意の天然又は合成トコフェロール、トコトリエノール、それらの任意の異性体、それらの任意のエステル、それらの任意のアナログ又は誘導体、又はそれらの任意の組合せを指す。

【０１４２】

【化１１】



【０１４３】

α－トコフェロール

ビタミンＥを備える化合物は抗酸化剤である。それらは、心臓病、癌、白内障、黄斑変性、緑内障、アルツハイマー病、及びパーキンソン病の症状を予防し、それらの発病を遅らせ、又は改善することができるという証拠もまた存在する。

【０１４４】

本発明は、ビタミンＥが、ベンゾジアゼピン薬にとって効果的な担体を供給できることを見出した。いくつかの実施形態において、ベンゾジアゼピンはビタミンＥに溶解できる、又は部分的に溶解できる。いくつかの実施形態において、ビタミンＥは、ミクロ粒子、ナノ粒子、又はそれらの任意の組合せとして存在し得る。更に、ビタミンＥの使用は、敏感な粘膜の炎症を回避すること、及び／又は、炎症を起こしている粘膜を落ち着かせることのいずれかの付加的な恩恵を有す。

【０１４５】

ビタミンＥは、一般的に疎水性に分類され、担体として用いられる時にはエマルションとしての製剤に限定され得る。しかしながら、エマルションは数個の欠点を有し得る。例えば、それらは作りだすのが困難であり、また非常に不安定であり得る。更に、それらは皮膚の表面上に、油の薄膜を残し得る。従って、エマルションの欠点を回避するため、本発明のいくつかの実施形態は、ビタミンＥと、１以上の低級アルキルアルコール又は１以上の低級アルキルグリコール、又はそれらの組合せ中の、１以上のベンゾジアゼピン薬の溶液を備える。

【０１４６】

低級アルキルアルコールは、６以下の炭素原子を有するものである。従って、エタノール、プロピルアルコール、ブチルアルコール、ペンタノール、ベンジルアルコール、それらの任意の異性体、又はそれらの任意の組合せのいずれかが、用いられ得る。

【０１４７】

低級アルキルグリコールは、６以下の炭素原子を有するものである。従って、エチレングリコール、プロピレングリコール、ブチレングリコール、ペンチレングリコール、それらの任意の異性体、又はそれらの任意の組合せのいずれかが、用いられ得る。

【０１４８】

追加の賦形剤

いくつかの実施形態において、組成物はベンゾジアゼピン薬、天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、及びアルコール又はグリコールに加えて、少なくとも１つの透過賦活剤を備える。いくつかの実施形態において、透過賦活剤は少なくとも１つのアルキルグリコシドである。いくつかの実施形態において、アルキルグリコシドは、任意の疎水性アルキルにつなぎ合わされる任意の糖を指し、このことは米国特許第５，６６１，１３０号に記されており、これは全体として参照することにより本明細書中に組み込まれる。疎水性アルキルは、任意の適切な長さであることができ、例えば、炭鎖長が約９から約２４の炭素、特に炭鎖長が約１０から約１４の炭素であり得る。疎水性アルキルは、分岐であり得、及び／又は部分的に又は全体的に不飽和であり得る。アルキルは例えばカルボニル基を介してサッカライドコアにつなぎ合わされ得、それによってエステル基が形成され得る。適切なアルキルグリコシドは、無毒性であり、非イオン性であり、本明細書中に記載されるように鼻腔内に投与されるとベンゾジアゼピン薬の吸収を増大させることができるという特徴を有する。本発明に係るアルキルに共有結合的につなぎ合わされ得る例示的な糖類は、グルコース、マルトース、マルトトリオース、マルトテトロース、スクロース、及びトレハロースを含む。使用され得る例示的なアルキルグリコシドは、オクチルー、ノニルー、デシルー、ウンデシルー、ドデシル、トリデシル、テトラデシル、ペンタデシル、オクタデシルα－又はβ－Ｄ－マルトシド、－グルコシド、又はスクロシドを含む。いくつかの実施形態において、好ましいグリコシドは、９、１０、１２、１４、１６、１８、又は２０炭素原子のアルキル鎖にグリコシド結合により連結される、マルトース、スクロース、又はグルコースを含む。本発明に従って経鼻組成物に使用され得る特定の賦形剤は、アルキルサッカライド（ａｌｋｙｌｓａｃｃｈａｒｉｄｅ）を含み、アルキルサッカライドは、ドデシルマルトシド、テトラデシルマルトシド、スクロースドデカノエイト、スクロースモノステアリン、スクロースジステアリン、及び／又は２又はそれより多いそれらの組合せを含む。本発明の実施形態において特に有用であるとみなされるアルキルグリコシドは、Ａｅｇｉｓ　Ｔｈｅｒａｐｅｕｔｉｃｓ，ＬＬＣ、サンディエゴ、カリホルニアよりＩｎｔｒａｖａｉｌ（登録商標）の名で販売されているものを含む。他のアルキルグリコシドは、親水性親油性バランス（ＨＬＢ）数が約１０から２０、特に約１１から１５を有するものから選択され得る。ＨＬＢ数は２００９年２月１９日に公開された、米国公開公報２００９／００４７３４７号に説明されるように決定され、この公報の全体、及び特に段落［００７５］から［００７９］は、参照することにより本明細書中に組み込まれる。存在する場合、組成物中のアルキルグリコシドの量は、鼻腔内経路により投与されるベンゾジアゼピン薬の吸収を高めるために十分な量である。いくつかの実施形態において、組成物中のアルキルグリコシドの量は、ベンゾジアゼピン薬の吸収を高めるために選択され、同時に鼻粘膜を著しく刺激しない。いくつかの実施形態において、組成物中のアルキルグリコシドの量は、約０．０１％（Ｗ／Ｖ）から約１％（Ｗ／Ｖ）までの範囲内である。いくつかの実施形態において、組成物中のアルキルグリコシドの量は、約０．０５％（Ｗ／Ｖ）から約０．５％（Ｗ／Ｖ）まで、又は約０．１２５％（Ｗ／Ｖ）から約０．５％（Ｗ／Ｖ）までの範囲内である。

【０１４９】

用語「透過賦活剤」は、粘膜を介する吸収を増大し、及び／又はバイオアベイラビリティを増大するよう作用する任意の物質を意味する。いくつかの実施形態において、このような物質は、粘液溶解薬、分解性酵素インヒビター、及び粘膜細胞膜の透過性を増大する化合物を含む。所与の化合物が「賦活剤」であるかどうかは、関連のない小さい極性分子を薬として備える、賦活剤を有し、又は有さない２つの製剤を、インビボ又は有効なモデル試験において、比較することにより、及び、薬の摂取が臨床的にかなりの程度まで高められるかどうかを決定することにより、決定される。賦活剤は、慢性毒性の点で、いかなる問題をももたらしてはならない、なぜなら、インビボで、賦活剤は非刺激的であるべきであり、及び／又は、任意の有意な刺激効果を有することなく通常の細胞構成要素に急速に代謝されるべきであるためである。

【０１５０】

いくつかの実施形態において、好ましい賦活物質、リゾリン脂質、例えば、卵又は大豆レシチンから得られるリゾホスファチジルコリンがある。異なるアシル基を有する他のリゾホスファチジルコリンや、同様の膜修飾特性を有する、ホスファチジルエタノールアミン及びホスファチジン酸から産生されるリゾ化合物が用いられ得る。アシルカルニチン（例えばパルミトイル－ｄｌ－カルニチン－クロライド）が選択肢である。いくつかの実施形態において、適切な濃度は０．０２％から２０％Ｗ／Ｖである。

【０１５１】

いくつかの実施形態において、ふさわしい賦活剤は、キレート化剤（ＥＧＴＡ、ＥＤＴＡ、アルギン酸塩）、界面活性剤（特に非イオン性の物質）、アシルグリセロール、脂肪酸及び塩、チロキサポール及び生物学的洗浄剤を含み、これらはシグマカタログ（ＳＩＧＭＡ　Ｃａｔａｌｏｇ）１９８８、ページ３１６から３２１に載っている（これは参照することにより本明細書中に組み込まれる）。また、膜流動性及び透過性を修飾する剤が適切であり、それらは、エナミン（例えば、エチルアセトアセテートのフェニルアラニンエナミン）、マロネート（例えば、ジエチレンオキシメチレンマロネート）サリチル酸塩、胆汁酸塩、及びアナログ並びにフシジン酸塩（ｆｕｓｉｄａｔｅｓ）などである。適切な濃度は、２０％Ｗ／Ｖまでである。

【０１５２】

従って、いくつかの実施形態において、本発明は、患者の１以上の鼻粘膜への投与用の薬学的に許容可能な製剤中に、約３０％から約９５％（Ｗ／Ｗ）までの量の、ベンゾジアゼピン薬、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、あるいはそれらの任意の組合せと、１以上のアルキルグリコシドと、約１０％から約７０％（Ｗ／Ｗ）までの量の、１以上のアルコール又はグリコール、もしくはそれらの任意の組合せとを備える、経鼻投与用の医薬組成物を提供する。いくつかの実施形態において、アルキルグリコシドはＩｎｔｒａｖａｉｌ（登録商標）ブランドのアルキルグリコシドである。いくつかの実施形態において、アルキルグリコシドは、ドデシルマルトシド、テトラデシルマルトシド、スクロースドデカノエイト、スクロースモノステアリン、スクロースジステアリン、及び／又は２以上のそれらの組合せである。いくつかの実施形態において、アルキルグリコシドは、ドデシルマルトシドである。いくつかの実施形態において、アルキルグリコシドは、テトラデシルマルトシドである。いくつかの実施形態において、アルキルグリコシドは、スクロースドデカノエイトである。いくつかの実施形態において、アルキルグリコシドは、スクロースモノステアリンである。いくつかの実施形態において、アルキルグリコシドは、スクロースジステアリンである。いくつかの実施形態において、アルキルグリコシドは、ドデシルマルトシド、テトラデシルマルトシド、スクロースドデカノエイト、スクロースモノステアリン、又はスクロースジステアリンの、２以上の組合せである。

【０１５３】

従って、いくつかの実施形態において、本発明は、患者の１以上の鼻粘膜への投与用の薬学的に許容可能な製剤中に、約３０％から約９５％（Ｗ／Ｗ）までの量の、ミクロ粒子、ナノ粒子又は両方を備えるベンゾジアゼピン薬、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、あるいはそれらの任意の組合せと、１以上のアルキルグリコシドと、約１０％から約７０％（Ｗ／Ｗ）までの量の、１以上のアルコール又はグリコール、もしくはそれらの任意の組合せとを備える、経鼻投与用の医薬組成物を提供する。いくつかの実施形態において、アルキルグリコシドはＩｎｔｒａｖａｉｌ（登録商標）ブランドのアルキルグリコシドである。いくつかの実施形態において、アルキルグリコシドは、ドデシルマルトシド、テトラデシルマルトシド、スクロースドデカノエイト、スクロースモノステアリン、スクロースジステアリン、及び／又は２以上のそれらの組合せである。いくつかの実施形態において、アルキルグリコシドは、ドデシルマルトシドである。いくつかの実施形態において、アルキルグリコシドは、テトラデシルマルトシドである。いくつかの実施形態において、アルキルグリコシドは、スクロースドデカノエイトである。いくつかの実施形態において、アルキルグリコシドは、スクロースモノステ

アリンである。いくつかの実施形態において、アルキルグリコシドは、スクロースジステアリンである。いくつかの実施形態において、アルキルグリコシドは、ドデシルマルトシド、テトラデシルマルトシド、スクロースドデカノエイト、スクロースモノステアリン、又はスクロースジステアリンの、２以上の組合せである。

【０１５４】

粘膜調製物

粘膜調製物は、２５０μＬ未満の、好ましくは１５０μＬ未満の、及び理想的には２５から１００μＬまでの容量を有する、計量スプレーで一般的に投与される。本発明で禁じられるものではないが、投与量当たり約３００μＬより大きい容量の投与は通常、膜の吸収能力を超える。これにより、薬学的に活性な成分の大部分が失われることとなる。

【０１５５】

調製物、特に鼻用調製物の投薬量の容量は、好ましくは２５から１００μＬに及ぶ。前記の範囲を超える容量は、その過剰分が嚥下されると、洞を迂回し、喉の後ろを流れ落ち得る。

【０１５６】

アルプラゾラム

アルプラゾラムの投薬量は、指示により異なるが、治療量は投与量あたり約０．５から約４まで、好ましくは約１から約２ｍｇまでの範囲内で、１日あたり１から８、好ましくは２から８、いくつかの好ましい実施形態においては約４から約６回の範囲内であることが予期される。アルプラゾラムは、米国特許第３，９８７，０５２号に開示される工程を用いて製造され、これは全体として参照することにより本明細書中に組み込まれる。

【０１５７】

経鼻製剤として、アルプラゾラムは、２５から２５０μＬの計量スプレーで投与され得る。いくつかの好ましい実施形態において、アルプラゾラムは、５０から１５０μＬ、特に約１００μＬの計量スプレーで投与される。

【０１５８】

ジアゼパム

ジアゼパムの投薬量は、指示により異なり得るが、しかしながら、治療量は投与量あたり約１から約２０まで、好ましくは約２から約１０ｍｇまでの範囲内で、１日あたり１から８、好ましくは２から８、いくつかの好ましい実施形態においては約４から約６回の範囲内であることが予期される。ジアゼパムは、米国特許第３，３７１，０８５号、第３，１０９，８４３号、第３，１３６，８１５号、又は第３，１０２，１１６号の１つに開示される工程を用いて製造され、これらのそれぞれは全体として参照することにより本明細書中に組み込まれる。

【０１５９】

経鼻製剤として、ジアゼパムは、２５から２５０μＬの計量スプレーで投与され得る。いくつかの好ましい実施形態において、ジアゼパムは、５０から１５０μＬ、特に約１００μＬの計量スプレーで投与される。

【０１６０】

フルラゼパム

フルラゼパムの投薬量は、指示により異なるが、治療量は投与量あたり約５から約４０まで、好ましくは約２０から約３５ｍｇまでの範囲内で、１日あたり１から８、好ましくは２から８、いくつかの好ましい実施形態においては約４から約６回の範囲内であることが予期される。フルラゼパムは、米国特許第３，５６７，７１０号、又は第３，２９９，０５３号の１つに開示される工程を用いて製造され、これらのそれぞれは全体として参照することにより本明細書中に組み込まれる。

【０１６１】

経鼻製剤として、フルラゼパムは、２５から２５０μＬの計量スプレーで投与され得る。いくつかの好ましい実施形態において、フルラゼパムは、５０から１５０μＬ、特に約１００μＬの計量スプレーで投与される。

【０１６２】
ロラゼパム
ロラゼパムの投薬量は、指示により異なるが、治療量は投与量あたり約０．１から約１０まで、好ましくは約０．２から約１ｍｇまでの範囲内で、１日あたり１から８、好ましくは２から８、いくつかの好ましい実施形態においては約４から約６回の範囲内であることが予期される。ロラゼパムは、米国特許第３，２９６，２４９号に開示される工程を用いて製造され、これは全体として参照することにより本明細書中に組み込まれる。
【０１６３】
経鼻製剤として、ロラゼパムは、２５から２５０μＬの計量スプレーで投与され得る。いくつかの好ましい実施形態において、ロラゼパムは、５０から１５０μＬ、特に約１００μＬの計量スプレーで投与される。
【０１６４】
メダゼパム
メダゼパムの投薬量は、指示により異なるが、治療量は投与量あたり約０．１から約１０まで、好ましくは約０．２から約１ｍｇまでの範囲内で、１日あたり１から８、好ましくは２から８、いくつかの好ましい実施形態においては約４から約６回の範囲内であることが予期される。メダゼパムは、米国特許第３，２４３，４２７号に開示される工程を用いて製造され、これは全体として参照することにより本明細書中に組み込まれる。
【０１６５】
経鼻製剤として、メダゼパムは、２５から２５０μＬの計量スプレーで投与され得る。いくつかの好ましい実施形態において、メダゼパムは、５０から１５０μＬ、特に約１００μＬの計量スプレーで投与される。
【０１６６】
メキサゾラム
メキサゾラムの投薬量は、指示により異なるが、治療量は投与量あたり約０．１から約１０まで、好ましくは約０．２から約１ｍｇまでの範囲内で、１日あたり１から８、好ましくは２から８、いくつかの好ましい実施形態においては約４から約６回の範囲内であることが予期される。メキサゾラムは、米国特許第３，７２２，３７１号に開示される工程を用いて製造され得、これは全体として参照することにより本明細書中に組み込まれる。
【０１６７】
経鼻製剤として、メキサゾラムは、２５から２５０μＬの計量スプレーで投与され得る。いくつかの好ましい実施形態において、メキサゾラムは、５０から１５０μＬ、特に約１００μＬの計量スプレーで投与される。
【０１６８】
ミダゾラム
ミダゾラムの投薬量は、指示により異なるが、治療量は投与量あたり約０．１から約２０まで、好ましくは約０．２から約１０ｍｇまでの範囲内で、１日あたり１から８、好ましくは２から８、いくつかの好ましい実施形態においては約４から約６回の範囲内であることが予期される。ミダゾラムは、米国特許第４，２８０，９５７号、又は第５，８３１，０８９号の一つに開示される工程を用いて製造され、これらのそれぞれは全体として参照することにより本明細書中に組み込まれる。
【０１６９】
経鼻製剤として、ミダゾラムは、２５から２５０μＬの計量スプレーで投与され得る。いくつかの好ましい実施形態において、ミダサゾラムは、５０から１５０μＬ、特に約１００μＬの計量スプレーで投与される。
【０１７０】
テマゼパム
テマゼパムの投薬量は、指示により異なるが、治療量は投与量あたり約１から約５０まで、好ましくは約５から約３０ｍｇまでの範囲内で、１日あたり１から８、好ましくは２から８、いくつかの好ましい実施形態においては約４から約６回の範囲内であることが予

期される。テマゼパムは、米国特許第３，３４０，２５３号、又は第３，３７４，２２５号に開示される工程を用いて製造され、これらのそれぞれは全体として参照することにより本明細書中に組み込まれる。

【０１７１】

経鼻製剤として、テマゼパムは、２５から２５０μＬの計量スプレーで投与され得る。いくつかの好ましい実施形態において、テマゼパムは、５０から１５０μＬ、特に約１００μＬの計量スプレーで投与される。

【０１７２】

製剤

いくつかの実施形態は、患者の１以上の粘膜に、治療的に効果的な量の１以上のベンゾジアゼピン薬、又はそれらの薬学的に許容可能な塩を投与することを備える。組成物のいくつかの実施形態は、１以上のベンゾジアゼピン薬、又はそれらの薬学的に許容可能な塩を、約６００ｍｇ／ｍＬまでの濃度で備える組成物を開示する。他の組成物は、１以上のベンゾジアゼピン薬、又はそれらの薬学的に許容可能な塩を、約１０ｍｇ／ｍＬから約２５０ｍｇ／ｍＬまでの濃度で備える組成物を開示する。更に、いくつかの実施形態は、１以上のベンゾジアゼピン薬、又はそれらの薬学的に許容可能な塩を、約２０ｍｇ／ｍＬから約５０ｍｇ／ｍＬまでの濃度で備える組成物を開示する。

【０１７３】

いくつかの実施形態は、約５０％から約９０％（Ｗ／Ｗ）のビタミンＥと約１０％から約５０％（Ｗ／Ｗ）の低級アルコール又は低級アルキルグリコール、又はそれらの任意の組合せである担体系を開示する。いくつかの実施形態は、約６５％から約７５％（Ｗ／Ｗ）のビタミンＥと約２５％から約３５％（Ｗ／Ｗ）の低級アルキルアルコール又は低級アルキルグリコール、又はそれらの任意の組合せである担体系を開示する。更にいくつかの実施形態は、約７０％（Ｗ／Ｗ）のビタミンＥと約３０％（Ｗ／Ｗ）の低級アルキルアルコール又は低級アルキルグリコール、又はそれらの任意の組合せである担体系を開示する。

【０１７４】

本発明のいくつかの実施形態は、ベンゾジアゼピン薬組成物を患者に投与する方法を提供する。好ましい実施形態は、ジアゼパムの使用を備える。方法のいくつかの実施形態は、所望の結果が達成されるまで、約１．０ｍｇから約２０．０ｍｇのジアゼパムの投薬量レベルを開示する。他の投薬量レベルは、所望の結果が達成されるまで約２．０ｍｇから約１５．０ｍｇの投薬量レベルを開示する。いくつかの実施形態は、所望の結果が達成されるまで、約５．０ｍｇから約１０．０ｍｇの投薬量レベルを開示する。

【０１７５】

方法のいくつかの実施形態において、投薬量容量は、約１０μＬから約２００μＬまでに及ぶ。いくつかの実施形態において、投薬量容量は、約２０μＬから約１８０μＬまでに及ぶ。更にいくつかの実施形態は、約５０μＬから約１４０μＬの投薬量容量を開示する。

【０１７６】

製剤工程

いくつかの実施形態において、経鼻投与用の組成物は、ベンゾジアゼピンミクロ粒子、ナノ粒子、又はそれらの組合せを実質的に有さない。いくつかの実施形態において、組成物はビタミンＥを液化するまでゆっくり温める又は熱することにより作られる。次に、１以上のベンゾジアゼピン薬が加えられる。混合物は、１以上のベンゾジアゼピン薬が溶解する又は実質的に溶解されるまで、撹拌され、熱せられる。次に、１以上のアルコールまたはグリコール、もしくはそれらの任意の組合せが、組成物に加えられる。組成物は、粘性の低い組成物が得られるまで撹拌される。

【０１７７】

前述の製剤は、好ましくは無菌であり、ｍｌ当たりとして、許容レベルを１０下回る細菌数を有する。加えて、病原体は好ましくは存在しない。

【０１７８】
いくつかの実施形態において、ベンゾジアゼピン薬は、ベンゾジアゼピンのミクロ粒子及び／又はナノ粒子懸濁液として処方される。ミクロ粒子及びナノ粒子ベンゾジアゼピンの調製は、製粉などの方法によって成し遂げられ得る。このような方法は、当該分野の当業者に知られている。
【０１７９】
いくつかの実施形態において、ベンゾジアゼピン薬は溶液として処方される。製剤を調製する工程の間、ミクロ粒子及び／又はナノ粒子ベンゾジアゼピン薬を使用することにより、溶媒系におけるベンゾジアゼピン薬の全体的な溶解度を改善することができることが、本発明の１つの態様として考慮される。
【０１８０】
追加の活性及び不活性成分
更に、組成物、及び組成物を使用する方法のいくつかの実施形態は、活性成分から選択される組成物中の追加の成分を備える。制約のない例として、このような活性成分は、インスリン、カルシトニン（例えば、豚の、ヒトの、サケの、ニワトリの、又はウナギの）及びそれらの合成修飾物、エンケファリン、ＬＨＲＨ及びアナログ（ナファレリン、ブセレリン、ゾリデックス（Ｚｏｌｉｄｅｘ））、ＧＨＲＨ（成長ホルモン放出ホルモン）、ニフェジピン、ＴＨＦ（胸腺液性因子）、ＣＧＲＰ（カルシトニン遺伝子関連ペプチド）、心房性ナトリウム利尿ペプチド、抗生物質、メトクロプラミド、エルゴタミン、ピゾチジン（Ｐｉｚｏｔｉｚｉｎ）、経鼻ワクチン（特にＨＩＶワクチン、麻疹、ライノウイルス１３型及び呼吸器合胞体ウイルス）、ペンタミジン、ＣＣＫ（コレシストキニン）、ＤＤＶＡＰ、インターフェロン、成長ホルモン（ソラトトロピア（ｓｏｌａｔｏｔｒｏｐｉｒ）ポリペプチド又はそれらの誘導体（好ましくは１０００から３００００までの分子量を有する）、セクレチン、ブラジキニンアンタゴニスト、ＧＲＦ（成長放出因子）、ＴＨＦ、ＴＲＨ（甲状腺刺激ホルモン放出ホルモン）、ＡＣＴＨアナログ、ＩＧＦ（インスリン様成長因子）、ＣＧＲＰ（カルシトニン遺伝子関連ペプチド）心房性ナトリウム利尿ペプチド、バソプレシン及びアナログ（ＤＤＡＶＰ、リプレシン）、メトクロプラミド、偏頭痛処置（ジヒドロエルゴタミン、エルゴメトリン、エルゴタミン、ピゾチジン（Ｐｉｚｏｔｉｚｉｎ））、経鼻ワクチン（特にエイズワクチン）第ＶＩＩＩ因子、コロニー刺激因子、Ｇ－ＣＳＦ（顆粒球コロニー刺激因子）、ＥＰＯ（エリスロポエチン）ＰＴＨ（副甲状腺ホルモン）又はそれらの薬学的に許容可能な塩、又はそれらの組合せを含む。
【０１８１】
更に、組成物、及び組成物を使用する方法のいくつかの実施形態は、他の抗痙攣薬から選択される組成物中の追加の成分を備える。制約のない例として、このような活性成分は、パラアルデヒド；芳香族アリルアルコール（スチリペントールなど）；バルビツール酸塩（例えば、フェノバルビトール（ｐｈｅｎｏｂａｒｂｉｔｏｌ）、プリミドン、メチルフェノバルビタール、メタルビタール及びバルベキサクロン）；臭化物（臭化カリウムなど）；カルバミン酸塩（フェルバメートなど）；カルボキサミド（カルバマゼピン及びオクスカルバゼピン）；脂肪酸（バルプロ酸、バルプロ酸ナトリウム、及びジバルプロエクスナトリウム、ビガバトリン、プロガビド、チアガビン）；フルクトース、トピラマート、ギャバ（Ｇａｂａ）アナログ（例えば、ガバペンチン及びプレガバリン）；ヒダントイン（例えばエトトイン、フェニトイン、メフェニトイン及びホスフェニトイン）；オキサゾリジンジオン（パラメタジオン、トリメタジオン、エタジオン）；プロピオン酸塩（例えばベクラミド）、ピリミジンジオン（例えばプリミドン）；ピロリジン（例えばブリバラセタム、レベチラセタム及びセレトラセタム）；コハク酸イミド（例えばエトスクシミド、フェンスクシミド及びメスクシミド）；スルホンアミド（例えばアセタゾラミド、スルチアム、メタゾラミド及びゾニサミド）；トリアジン（ラモトリジンなど）；尿素（フェネツリド、フェナセミド）；バルプロイルアミド（ｖａｌｐｒｏｙｌａｍｉｄｅｓ）（バルプロミド及びバルノクタミド）；及び他の抗痙攣薬、又は薬学的に許容可能な塩又はそれらの組合せを含む。

【０１８２】
更に、組成物、及び組成物を使用する方法のいくつかの実施形態は、他の抗痙攣薬から選択される組成物中の追加の成分を備える。制約のない例として、このような活性成分は、テトラサイクリン塩酸塩、ロイコマイシン、ペニシリン、ペニシリン誘導体、エリスロマイシン、ゲンタマイシン、スルファチアゾール及びニトロフラゾンなどの抗生物質及び抗菌剤；ベンゾカインなどの局所麻酔剤；フェニレフリン塩酸塩、塩酸テトラヒドロゾリン、硝酸ナファゾリン、塩酸オキシメタゾリン及びトラマゾリン塩酸塩などの血管収縮剤；ジギタリス及びジゴキシンなどの強心剤；ニトログリセリン及びパパベリン塩酸塩などの血管拡張剤；塩酸クロルヘキシジン、ヘキシルレゾルシノール、塩化デカリニウム及びエタクリジンなどの消毒剤；塩化リゾチーム、デキストラナーゼなどの酵素；ビタミンＤ、活性ビタミンＤ及びビタミンＣなどの骨代謝調節剤；性ホルモン；降圧剤；鎮静剤；抗腫瘍薬；ヒドロコルチゾン、プレドニゾン、フルチカゾン、プレドニゾロン、トリアムシノロン、トリアムシノロンアセトニド、デキサメタゾン、ベタメタゾン、ベクロメタゾン、及びジプロピオン酸ベクロメタゾンなどのステロイド性抗炎症剤；アセトアミノフェン、アスピリン、アミノピリン、フェニルブタゾン、メダナミック（ｍｅｄａｎａｍｉｃ）酸、イブプロフェン、ジクロフェナクナトリウム、インドメタシン（ｉｎｄｏｍｅｔｈａｃｉｎｅ）、コルヒチン、及びプロベノシド（ｐｒｏｂｅｎｏｃｉｄ）などの非ステロイド性抗炎症剤；キモトリプシン及びブロメラインセラチオペプチダーゼ（ｂｒｏｍｅｌａｉｎ　ｓｅｒａｔｉｏｐｅｐｔｉｄａｓｅ）などの酵素的な抗炎症剤；塩酸ジフェンヒドラミン、クロロフェニラミンマレイン酸塩（ｃｈｌｏｒｏｐｈｅｎｉｒａｍｉｎｅ　ｍａｌｅａｔｅ）及びクレマスチンなどの抗ヒスタミン剤；クロモグリク酸ナトリウム、コデインリン酸塩、及び塩酸イソプロテレノールなどの抗アレルギー剤及び鎮咳－去痰、抗ぜんそく薬、又はそれらの薬学的に許容可能な塩又はそれらの組合せを含む。

【０１８３】
更に、組成物、及び組成物を使用する方法のいくつかの実施形態は、組成物中の追加の不活性成分を備える。制約のない例として、安定剤、着色剤、ｐＨ調整剤、緩衝剤、分解を防ぎ得る薬剤などの保存剤、湿潤剤、及び香味剤などの少量の成分もまた存在し得る。着色剤の例には、β－カロチン、赤色２号及び青色１号が含まれる。保存剤の例にはステアリン酸、ステアリン酸アスコルビル及びアスコルビン酸が含まれる。矯味薬の例には、メントール及び柑橘類香料が含まれる。

【０１８４】
いくつかの実施形態において、本発明の薬送達システムは、好都合に吸収賦活剤を備える。用語「賦活剤」は、粘膜を介する吸収を増大し、及び／又は、バイオアベイラビリティを増大させるよう作用する任意の物質を意味する。いくつかの実施形態において、このような物質は、粘液溶解薬、分解性酵素インヒビター、及び粘膜細胞膜の透過性を増大する化合物を含む。所与の化合物が「賦活剤」であるかどうかは、関連のない小さい極性分子を薬として備える、賦活剤を有し、又は有さない２つの製剤を、インビボ又は有効なモデル試験において、比較することにより決定され、薬の摂取が臨床的にかなりの程度まで高められるかどうかを決定することにより決定される。賦活剤は、慢性毒性の点で、いかなる問題をももたらしてはならない、なぜなら、インビボで、賦活剤は非刺激的であるべきであり、及び／又は、任意の有意の刺激効果を有さない正常な細胞構成要素に急速に代謝されるべきである。

【０１８５】
いくつかの実施形態において、好ましい賦活物質、リゾリン脂質、例えば、卵又は大豆レシチンから得られるリゾホスファチジルコリンがある。異なるアシル基を有する他のリゾホスファチジルコリンや、ホスファチジルエタノールアミン及びホスファチジン酸から産生され、同様の膜修飾特性を有するリゾ化合物が用いられ得る。アシルカルニチン（例えばパルミトイル－ｄｌ－カルニチン－クロライド）が選択肢である。いくつかの実施形態において、適切な濃度は０．０２％から２０％Ｗ／Ｖである。

【０１８６】

いくつかの実施形態において、ふさわしい賦活剤は、キレート化剤（ＥＧＴＡ、ＥＤＴＡ、アルギン酸塩）、界面活性剤（特に非イオン性の物質）、アシルグリセロール、脂肪酸及び塩、チロキサポール及び生物学的洗浄剤を含み、これらはシグマカタログ（ＳＩＧＭＡ　Ｃａｔａｌｏｇ）１９８８、ページ３１６から３２１に載っている（これは参照することにより本明細書中に組み込まれる）。また、膜流動性及び透過性を修飾する剤が適切であり、それらは、エナミン（例えば、エチルアセトアセテートのフェニルアラニンエナミン）、マロネート（例えば、ジエチレンオキシメチレンマロネート）、サリチル酸塩、胆汁酸塩、及びアナログ並びにフシジン酸塩（ｆｕｓｉｄａｔｅｓ）などである。適切な濃度は、２０％Ｗ／Ｖまでである。

【０１８７】

いくつかの実施形態において、本発明は、追加の薬学的アジュバントを備える生体接着ミクロスフェア中に又は生体接着ミクロスフェア上に組み込まれる薬の送達を利用し、活性薬及び粘液溶解薬、ペプチダーゼインヒビター又は非薬物ポリペプチド基質を単独で又は組合せで含有するシステムに適用する。適宜、粘液溶解薬は、Ｎ－アセチルシステイン、及びその誘導体などのチオール含有化合物である。ペプチドインヒビタには、アクチノニン、アマスタチン、ベスタチン、クロロアセチル－ＨＯＬｅｕ－Ａｌａ－Ｇｌｙ－ＮＨ．ｓｕｂ．２、ジプロチンＡ及びＢ、エベラクトンＡ及びＢ、Ｅ－６４、ロイペプチン、ペプスタチンＡ、ホスホラミドン、Ｈ－Ｔｈｒ－（ｔＢｕ）－Ｐｈｅ－Ｐｒｏ－ＯＨ、アプロチニン、カリクレイン、キモスタチン、ベンズアミジン、キモトリプシン及びトリプシンが含まれる。適切な濃度は、０．０１％から１０％Ｗ／Ｖである。当該分野の当業者は、賦活剤が含まれるべきかどうかを容易に決定することができる。

【０１８８】

投与

いくつかの実施形態において、組成物の投与は、治療的に効果的な量の組成物の少なくとも一部を、少なくとも１つの粘膜上に投与することを備える。いくつかの実施形態において、組成物の投与は、治療的に効果的な量の組成物の少なくとも一部を、少なくとも１つの鼻孔中に噴霧することを備える。いくつかの実施形態において、組成物の投与は、治療的に効果的な量の組成物の少なくとも一部を、それぞれの鼻孔中に噴霧することを備える。いくつかの実施形態において、組成物の投与は、組成物の第１の量を第１の鼻孔中に噴霧すること、組成物の第２の量を第２の鼻孔中に噴霧すること、及び任意に事前に選択した時間遅延の後、組成物の第３の量を第１の鼻孔中に噴霧することを備える。いくつかの実施形態は、任意に事前に選択した時間遅延の後、少なくとも組成物の第４の量を第２の鼻孔中に投与することを更に備える。

【０１８９】

アルプラゾラム

アルプラゾラムの投薬量は、指示により異なるが、治療量は投与量あたり約０．５から約４まで、好ましくは約１から約２ｍｇまでの範囲内で、１日あたり１から８、好ましくは２から８、いくつかの好ましい実施形態においては約４から約６回の範囲内であることが予期される。アルプラゾラムは、米国特許第３，９８７，０５２号に開示される工程を用いて製造され、これは全体として参照することにより本明細書中に組み込まれる。

【０１９０】

経鼻製剤として、アルプラゾラムは、２５から２５０μＬの計量スプレーで投与され得る。いくつかの好ましい実施形態において、アルプラゾラムは、５０から１５０μＬ、特に約１００μＬの計量スプレーで投与される。いくつかの実施形態において、第１の計量スプレーは第１の鼻孔に適用され、必要であれば第２の計量スプレーが第２の鼻孔に適用される。いくつかの任意の実施形態において、第３の計量スプレーが第１の鼻孔に適用される。いくつかの実施形態において、第４の計量スプレーが第２の鼻孔に適用される。いくつかの実施形態において、患者に全ての標的治療量が投与されるまで、追加の計量スプレーが、交互の鼻孔に適用される。いくつかの実施形態において、ベンゾジアゼピン薬の同じ鼻孔への適用の間に、数秒から５分間、好ましくは約１０秒から約１分間の時間の増

加分がある。これにより、薬が鼻粘膜を通過し、血流中に入る時間が与えられる。任意に時間間隔で区切る、それぞれの鼻孔への計量スプレーの多数回適用は、ベンゾジアゼピン薬を血流中に全て吸収することを可能にするために十分少しずつ、全治療量を投与することを可能とし、喉の奥の下への薬の損失を避けることができる。

【０１９１】

ジアゼパム

ジアゼパムの投薬量は、指示により異なり得るが、しかしながら、治療量は投与量あたり約１から約２０まで、好ましくは約２から約１０ｍｇまでの範囲内で、１日あたり１から８、好ましくは２から８、いくつかの好ましい実施形態においては約４から約６回の範囲内であることが予期される。ジアゼパムは、米国特許第３，３７１，０８５号、第３，１０９，８４３号、第３，１３６，８１５号、又は第３，１０２，１１６号の１つに開示される工程を用いて製造され、これらのそれぞれは全体として参照することにより本明細書中に組み込まれる。

【０１９２】

経鼻製剤として、ジアゼパムは、２５から２５０μＬの計量スプレーで投与され得る。いくつかの好ましい実施形態において、ジアゼパムは、５０から１５０μＬ、特に約１００μＬの計量スプレーで投与される。いくつかの実施形態において、第１の計量スプレーは第１の鼻孔に適用され、必要であれば第２の計量スプレーが第２の鼻孔に適用される。いくつかの任意の実施形態において、第３の計量スプレーが第１の鼻孔に適用される。いくつかの実施形態において、第４の計量スプレーが第２の鼻孔に適用される。いくつかの実施形態において、患者に全ての標的治療量が投与されるまで、追加の計量スプレーが、交互の鼻孔に適用される。いくつかの実施形態において、ベンゾジアゼピン薬の同じ鼻孔への適用の間に、数秒から５分間、好ましくは約１０秒から約１分間の時間の増加分がある。これにより、薬が鼻粘膜を通過し、血流中に入る時間が与えられる。任意に時間間隔で区切り、それぞれの鼻孔への計量スプレーの多数回適用は、ベンゾジアゼピン薬を血流中に全て吸収することを可能にするために十分少しずつ、全治療量を投与することを可能とし、喉の奥の下への薬の損失を避けることができる。

【０１９３】

フルラゼパム

フルラゼパムの投薬量は、指示により異なるが、治療量は投与量あたり約５から約４０まで、好ましくは約２０から約３５ｍｇまでの範囲内で、１日あたり１から８、好ましくは２から８、いくつかの好ましい実施形態においては約４から約６回の範囲内であることが予期される。フルラゼパムは、米国特許第３，５６７，７１０号、又は第３，２９９，０５３号の１つに開示される工程を用いて製造され、これらのそれぞれは全体として参照することにより本明細書中に組み込まれる。

【０１９４】

経鼻製剤として、フルラゼパムは、２５から２５０μＬの計量スプレーで投与され得る。いくつかの好ましい実施形態において、フルラゼパムは、５０から１５０μＬ、特に約１００μＬの計量スプレーで投与される。いくつかの実施形態において、第１の計量スプレーは第１の鼻孔に適用され、必要であれば第２の計量スプレーが第２の鼻孔に適用される。いくつかの任意の実施形態において、第３の計量スプレーが第１の鼻孔に適用される。いくつかの実施形態において、第４の計量スプレーが第２の鼻孔に適用される。いくつかの実施形態において、患者に全ての標的治療量が投与されるまで、追加の計量スプレーが、交互の鼻孔に適用される。いくつかの実施形態において、ベンゾジアゼピン薬の同じ鼻孔への適用の間に、数秒から５分間、好ましくは約１０秒から約１分間の時間の増加分がある。これにより、薬が鼻粘膜を通過し、血流中に入る時間が与えられる。任意に時間間隔で区切る、それぞれの鼻孔への計量スプレーの多数回適用は、ベンゾジアゼピン薬を血流中に全て吸収することを可能にするために十分少しずつ、全治療量を投与することを可能とし、喉の奥の下への薬の損失を避けることができる。

【０１９５】

ロラゼパム

ロラゼパムの投薬量は、指示により異なるが、治療量は投与量あたり約０．１から約１０まで、好ましくは約０．２から約１ｍｇまでの範囲内で、１日あたり１から８、好ましくは２から８、いくつかの好ましい実施形態においては約４から約６回の範囲内であることが予期される。ロラゼパムは、米国特許第３，２９６，２４９号に開示される工程を用いて製造され、これは全体として参照することにより本明細書中に組み込まれる。

【０１９６】

経鼻製剤として、ロラゼパムは、２５から２５０μＬの計量スプレーで投与され得る。いくつかの好ましい実施形態において、ロラゼパムは、５０から１５０μＬ、特に約１００μＬの計量スプレーで投与される。いくつかの実施形態において、第１の計量スプレーは第１の鼻孔に適用され、必要であれば第２の計量スプレーが第２の鼻孔に適用される。いくつかの任意の実施形態において、第３の計量スプレーが第１の鼻孔に適用される。いくつかの実施形態において、第４の計量スプレーが第２の鼻孔に適用される。いくつかの実施形態において、患者に全ての標的治療量が投与されるまで、追加の計量スプレーが、交互の鼻孔に適用される。いくつかの実施形態において、ベンゾジアゼピン薬の同じ鼻孔への適用の間に、数秒から５分間、好ましくは約１０秒から約１分間の時間の増加分がある。これにより、薬が鼻粘膜を通過し、血流中に入る時間が与えられる。任意に時間間隔で区切る、それぞれの鼻孔への計量スプレーの多数回適用は、ベンゾジアゼピン薬を血流中に全て吸収することを可能にするために十分少しずつ、全治療量を投与することを可能とし、喉の奥の下への薬の損失を避けることができる。

【０１９７】

メダゼパム

メダゼパムの投薬量は、指示により異なるが、治療量は投与量あたり約０．１から約１０まで、好ましくは約０．２から約１ｍｇまでの範囲内で、１日あたり１から８、好ましくは２から８、いくつかの好ましい実施形態においては約４から約６回の範囲内であることが予期される。メダゼパムは、米国特許第３，２４３，４２７号に開示される工程を用いて製造され、これは全体として参照することにより本明細書中に組み込まれる。

【０１９８】

経鼻製剤として、メダゼパムは、２５から２５０μＬの計量スプレーで投与され得る。いくつかの好ましい実施形態において、メダゼパムは、５０から１５０μＬ、特に約１００μＬの計量スプレーで投与される。いくつかの実施形態において、第１の計量スプレーは第１の鼻孔に適用され、必要であれば第２の計量スプレーが第２の鼻孔に適用される。いくつかの任意の実施形態において、第３の計量スプレーが第１の鼻孔に適用される。いくつかの実施形態において、第４の計量スプレーが第２の鼻孔に適用される。いくつかの実施形態において、患者に全ての標的治療量が投与されるまで、追加の計量スプレーが、交互の鼻孔に適用される。いくつかの実施形態において、ベンゾジアゼピン薬の同じ鼻孔への適用の間に、数秒から５分間、好ましくは約１０秒から約１分間の時間の増加分がある。これにより、薬が鼻粘膜を通過し、血流中に入る時間が与えられる。任意に時間間隔で区切る、それぞれの鼻孔への計量スプレーの多数回適用は、ベンゾジアゼピン薬を血流中に全て吸収することを可能にするために十分少しずつ、全治療量を投与することを可能とし、喉の奥の下への薬の損失を避けることができる。

【０１９９】

メキサゾラム

メキサゾラムの投薬量は、指示により異なるが、治療量は投与量あたり約０．１から約１０まで、好ましくは約０．２から約１ｍｇまでの範囲内で、１日あたり１から８、好ましくは２から８、いくつかの好ましい実施形態においては約４から約６回の範囲内であることが予期される。メキサゾラムは、米国特許第３，７２２，３７１号に開示される工程を用いて製造され、これは全体として参照することにより本明細書中に組み込まれる。

【０２００】

経鼻製剤として、メキサゾラムは、２５から２５０μＬの計量スプレーで投与され得る

。いくつかの好ましい実施形態において、メキサゾラムは、５０から１５０μＬ、特に約１００μＬの計量スプレーで投与される。いくつかの実施形態において、第１の計量スプレーは第１の鼻孔に適用され、必要であれば第２の計量スプレーが第２の鼻孔に適用される。いくつかの任意の実施形態において、第３の計量スプレーが第１の鼻孔に適用される。いくつかの実施形態において、第４の計量スプレーが第２の鼻孔に適用される。いくつかの実施形態において、患者に全ての標的治療量が投与されるまで、追加の計量スプレーが、交互の鼻孔に適用される。いくつかの実施形態において、ベンゾジアゼピン薬の同じ鼻孔への適用の間に、数秒から５分間、好ましくは約１０秒から約１分間の時間の増加分がある。これにより、薬が鼻粘膜を通過し、血流中に入る時間が与えられる。任意に時間間隔で区切る、それぞれの鼻孔への計量スプレーの多数回適用は、ベンゾジアゼピン薬を血流中に全て吸収することを可能にするために十分少しずつ、全治療量を投与することを可能とし、喉の奥の下への薬の損失を避けることができる。

【０２０１】

ミダゾラム

ミダゾラムの投薬量は、指示により異なるが、治療量は投与量あたり約０．１から約２０まで、好ましくは約０．２から約１０ｍｇまでの範囲内で、１日あたり１から８、好ましくは２から８、いくつかの好ましい実施形態においては約４から約６回の範囲内であることが予期される。ミダゾラムは、米国特許第４，２８０，９５７号、又は第５，８３１，０８９号の一つに開示される工程を用いて製造され、これらのそれぞれは全体として参照することにより本明細書中に組み込まれる。

【０２０２】

経鼻製剤として、ミダゾラムは、２５から２５０μＬの計量スプレーで投与され得る。いくつかの好ましい実施形態において、ミダゾラムは、５０から１５０μＬ、特に約１００μＬの計量スプレーで投与される。いくつかの実施形態において、第１の計量スプレーは第１の鼻孔に適用され、必要であれば第２の計量スプレーが第２の鼻孔に適用される。いくつかの任意の実施形態において、第３の計量スプレーが第１の鼻孔に適用される。いくつかの実施形態において、第４の計量スプレーが第２の鼻孔に適用される。いくつかの実施形態において、患者に全ての標的治療量が投与されるまで、追加の計量スプレーが、交互の鼻孔に適用される。いくつかの実施形態において、ベンゾジアゼピン薬の同じ鼻孔への適用の間に、数秒から５分間、好ましくは約１０秒から約１分間の時間の増加分がある。これにより、薬が鼻粘膜を通過し、血流中に入る時間が与えられる。任意に時間間隔で区切る、それぞれの鼻孔への計量スプレーの多数回適用は、ベンゾジアゼピン薬を血流中に全て吸収することを可能にするために十分少しずつ、全治療量を投与することを可能とし、喉の奥の下への薬の損失を避けることができる。

【０２０３】

テマゼパム

テマゼパムの投薬量は、指示により異なるが、治療量は投与量あたり約１から約５０まで、好ましくは約５から約３０ｍｇまでの範囲内で、１日あたり１から８、好ましくは２から８、いくつかの好ましい実施形態においては約４から約６回の範囲内であることが予期される。テマゼパムは、米国特許第３，３４０，２５３号、又は第３，３７４，２２５号に開示される工程を用いて製造され、これらのそれぞれは全体として参照することにより本明細書中に組み込まれる。

【０２０４】

経鼻製剤として、テマゼパムは、２５から２５０μＬの計量スプレーで投与され得る。いくつかの好ましい実施形態において、テマゼパムは、５０から１５０μＬ、特に約１００μＬの計量スプレーで投与される。いくつかの実施形態において、第１の計量スプレーは第１の鼻孔に適用され、必要であれば第２の計量スプレーが第２の鼻孔に適用される。いくつかの任意の実施形態において、第３の計量スプレーが第１の鼻孔に適用される。いくつかの実施形態において、第４の計量スプレーが第２の鼻孔に適用される。いくつかの実施形態において、患者に全ての標的治療量が投与されるまで、追加の計量スプレーが、

交互の鼻孔に適用される。いくつかの実施形態において、ベンゾジアゼピン薬の同じ鼻孔への適用の間に、数秒から５分間、好ましくは約１０秒から約１分間の時間の増加分がある。これにより、薬が鼻粘膜を通過し、血流中に入る時間が与えられる。任意に時間間隔で区切る、それぞれの鼻孔への計量スプレーの多数回適用は、ベンゾジアゼピン薬を血流中に全て吸収することを可能にするために十分少しずつ、全治療量を投与することを可能とし、喉の奥の下への薬の損失を避けることができる。

【０２０５】

当該分野の当業者は、前述の疾患を処置するためのベンゾジアゼピン薬の、体系的な治療的に効果的な量は、疾病の重症度だけでなく、患者の年齢、大きさ、体重、及び一般的な健康状態によって異なるということを承知している。投与の頻度も同様に、組成物の製剤によって異なり、１日当たり任意の数の投与量が用いられるよう調整されることができる。

【０２０６】

実施例

本発明はこれより、以下の例示的な、非限定の実施例を参照して示される。

【０２０７】

実施例１

ジアゼパムを備える医薬組成物が調製される。それは経鼻送達装置を介して送達されるための溶液として処方される。組成物は、成人のてんかんと関連する発作を処置又は予防するために用いられる。処置は、発作が始まった前又は後のいずれかで実施される。患者が発病している場合、それは、任意の経鼻送達装置からの１パフ（５．０ｍｇ／パフ（５．０ｍｇ／０．１ｍＬ、及び、０．１ｍＬ／パフ）で１パフ）として、５分毎に、発作の停止まで投与される。しかしながら、それは、それぞれの鼻孔中に鼻孔当たり１パフ（２．５ｍｇ／パフ（５．０ｍｇ／０．１ｍＬ、及び、０．０５ｍＬ／パフ）で２パフ）として、５分毎に、発作の停止まで与えられ得る。この実施例による組成物は、以下の表に示される。

【０２０８】

【表１】

表 1-1

5.0 mg/0.1mL	ジアゼパム
70.0 mg	α-トコフェロール
0.1 mL	エタノール(適量0.1mLまで)

【０２０９】

実施例２

ジアゼパムを備える医薬組成物が調製される。それは、経鼻送達装置を介して送達されるための溶液として処方される。組成物は、小児のてんかんと関連する発作を処置又は予防するために用いられる。処置は発作が始まった前又は後のいずれかで実施される。患者が発病している場合、それは、経鼻送達装置からの１パフ（２．０ｍｇ／パフ（２．０ｍｇ／０．１ｍＬ、及び、０．１ｍＬ／パフ）で１パフ）として投与される。発作が中止しない場合、５分後もう１投与量が投与され得る。しかしながら、それは、それぞれの鼻孔中に鼻孔当たり１パフ（１．０ｍｇ／パフ（２．０ｍｇ／０．１ｍＬ、及び、０．０５ｍＬ／パフ）で２パフ）として与えられることができる。発作が中止しない場合、５分後もう１投与量が投与され得る。この例による組成物は以下の表に示される。

【０２１０】

【表２】

表 2-1

2.0 mg/0.1mL	ジアゼパム
70.0 mg	α-トコフェロール
0.1 mL	エタノール (適量0.1mLまで)

【０２１１】
実施例３－ジアゼパム溶液の製剤
一般的に、ベンゾジアゼピン溶液は、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノールと１以上の低級アルコール又はグリコールを混合して、均一混合物が形成されるまで混ぜ合わせ、その均一混合物にベンゾジアゼピン薬を加え、ベンゾジアゼピン薬が均一混合物中に完全に溶解するまで成分を熱し及び混ぜ合わせ、混合物を冷却し、混合物を低級アルコール又はグリコールで、最終質量又は容量へともたらすことにより処方され得る。
【０２１２】
前述の工程により、２つの異なるジアゼパム溶液が処方された。ビタミンＥ　ＵＳＰ及び無水エタノール　ＵＳＰが以下の表に示される量で加えられ、混ぜ合わされることにより均一混合物を形成した。以下の表に示される量のジアゼパムがその後、均一混合物に加えられた。成分は、ジアゼパムが完全に溶解するまで、４０から４５℃に混ぜ合わせながら熱せられ、その結果溶液を形成した。溶液は２０から２５℃に冷却され、その結果溶液は無水エタノール　ＵＳＰを用いて最終標的重量となり、溶液は均一性を確実にするため完全に混ぜ合わされた。溶液はその後製造工程の試験用にサンプル抽出され、３ｍＬの琥珀色のガラスバイアルに入れられた。
【０２１３】
【表３】

表3-1: ジアゼパム溶液－70 mg/mL

構成要素	溶液 00 (65% ビタミン E) 濃度 (mg/mL)	溶液 02 (80% ビタミン E) 濃度 (mg/mL)
ジアゼパム USP	70.0	70.0
ビタミン E USP	650.0	800.0
無水エタノール USP	適量1mLまで	適量1mLまで

【０２１４】
ジアゼパムの量と、ビタミンＥ及びエタノールの相対量を変えることにより、追加の様々な濃度のジアゼパム溶液が同様の方法で作られる。他のベンゾジアゼピン溶液は、ジアゼパムの代わりに１以上のベンゾジアゼピンを使うことにより作られる。アルキルグリコシドなどの他の成分が、工程の適切な段階で（例えば、ベンゾジアゼピンの添加の前又は添加と同時に）加えられ得る。
【０２１５】
実施例４－ジアゼパム懸濁液の製剤
一般的に、ベンゾジアゼピン懸濁液は、ベンゾジアゼピンを微粒子化し、ベンゾジアゼピンを担体と混合することにより処方される。担体は、１以上の低級アルコール又はグリ

コールを水と混合し、天然又は合成トコフェロールもしくは天然又は合成トコトリエノールを加え、トコフェロール又はトコトリエノールが溶解するまで混合物を熱し、１以上のパラベンを加えてパラベンが溶解するまで混ぜ合わせ担体を冷却することにより、調製される。ベンゾジアゼピンが担体に加えられるとすぐに、界面活性剤などの追加の賦形剤が任意に加えられ、担体中に溶解されることができる。懸濁液はその後、水を用いて最終質量又は容量へともたらされる。

【０２１６】

２つの異なるベンゾジアゼピン懸濁液が、前述の一般的な工程により処方された。２つの異なるジアゼパムの粒径が調製され、それらは、Ａ：高圧微粒子化により調製される小さい粒径、及びＢ：低圧微粒子化により調製される大きい粒径である。担体は、プロピレングリコールＵＳＰと、精製水ＵＳＰとを混合し、その後ビタミンＥポリエチレングリコールスクシネートＮＦを加え、その後混合された成分を約４５℃に混ぜ合わせ及び熱することにより調製された。混ぜ合わせることはビタミンＥポリエチレングリコールスクシネートが完全に溶解するまで続けられた。担体はその後、２０から２５℃に冷却された。微粒子化されたジアゼパム（Ａ及びＢ）はその後担体に加えられ、ジアゼパムが完全に担体中に分散するまで強く混ぜ合わされた。ポリビニルピロリドンポビドンＵＳＰ／ＮＦがその後混合物に加えられ、完全に溶解するまで混ぜ合わされた。懸濁液はその後、精製水ＵＳＰを用いて重量へともたらされた。懸濁液はその後、均一になるまで混ぜ合わされ、製造工程の試験用にサンプル抽出され、３ｍＬの琥珀色のガラスバイアルに入れられた。

【０２１７】

【表４】

表4-1: ジアゼパム懸濁液製剤

構成要素	懸濁液 03 (200 mg/mL ジアゼパム) 濃度 (mg/mL)	懸濁液 01 (100 mg/mL ジアゼパム) 濃度 (mg/mL)
ジアゼパム USP	200.00	100.00
ビタミンEポリエチレングリコールスクシネート NF	100.0	100.0
メチルパラベン NF	2.0	2.0
プロピルパラベン NF	0.5	0.5
プロピレングリコール USP	100.0	100.0
ポビドン USP/NF	25.0	25.0
精製水 USP/EP	適量1mLまで	適量1mLまで

【０２１８】

ジアゼパム及び任意に他の賦形剤の量を変えることにより、追加の様々な濃度のジアゼパムの懸濁液が、同様の方法で作られる。他のベンゾジアゼピン懸濁液は、ジアゼパムの代わりに１以上のベンゾジアゼピンを使うことにより作られる。アルキルグリコシドなどの他の成分が、工程の適切な段階で加えられることができる。例えば、アルキルグリコシドは、担体の配合中に担体に加えられ得、又はポビドンの添加と同時、或いは添加後に懸濁液混合物に加えられ得る。

【０２１９】

実施例５－ジアゼパム溶液及び懸濁液の安定性

溶液００及び０２（実施例３）及び懸濁液０１及び０３（実施例４）が、２５℃／６０ＲＨ、３０℃／６５％ＲＨ、及び４０℃／７５％ＲＨで安定した状態で提示された。４つの異なる製剤のそれぞれ１回分が、３ｍｌのねじ蓋式の蓋を有するバイアルに入れられ、対応するアクチュエーターとともに、３つの保存条件で提示された。それらは、それらの

対応するＰａｒｔｉｃｌｅ　Ｓｃｉｅｎｃｅの初期サンプル管理番号とともに、表１に列挙される。

【０２２０】

【表５】

表5-1： PSIサンプル管理番号の概要

製剤 #	25°C/60% RH	30°C/65% RH	40°C/75% RH
溶液 00 – 70 mg/ml 溶液 , 65% ビタミン E	083101.01	083101.02	083101.02
溶液 02 – 70 mg/ml 溶液 , 80% ビタミン E	083102.01	083102.02	083102.03
懸濁液 01 - 100 mg/ml 懸濁液	083103.01	083103.02	083103.03
懸濁液 03 - 200 mg/ml 懸濁液	083104.01	083104.02	083104.03

【０２２１】

サンプルは、スプレー内容物の均一性、スプレー容量、ジアゼパム含有量、ジアゼパム関連物質、及びメチルパラベン並びにプロピルパラベンアッセイ（懸濁液サンプルのみ）を試験された。単位重量はＵＳＰ＜７５５＞毎として決定された。

【０２２２】

平均アッセイ値の概要及び他の全ての結果は、表５－４、５－５、５－６、及び５－７に与えられる。開始時点、１カ月及び３カ月時点での結果もまた、比較のために示される。個別のスプレー内容物の均一性の結果は、表５－８、５－９、５－１０、５－１１、５－１２、５－１３、５－１４、及び５－１５に与えられる。

【０２２３】

一般的に、アッセイの全て及び他の結果は、ジアゼパム関連化合物Ａ及びＢを除いて、初期データと同様である。

【０２２４】

関連化合物Ａは、いくつかのサンプルについて、多くて（ＮＭＴ）０．０１％という仕様を満たさなかった（表２を参照）。関連化合物Ａは、時間及び温度とともに増大した。

【０２２５】

【表６】

表5-2: 関連化合物A T6M結果の概要

溶液/懸濁液 #	25°C/60% RH	30°C/65% RH	40°C/75% RH
溶液 00	仕様を満たす	0.058%	0.051%
溶液 02	仕様を満たす	仕様を満たす	仕様を満たす
懸濁液 01	0.038%	0.046%	0.157%
懸濁液 03	0.019%	0.029%	0.081%

【０２２６】

関連化合物Ｂもまた、時間及び温度とともに増大しており、現状では懸濁液及び１つの溶液製剤の両方について、４０℃でＮＭＴ０．１％の仕様に満たない。製剤２６０２のみが、全ての不純物の仕様を満たす。

【０２２７】
【表７】

表5-3: 関連化合物B T6M結果の概要

溶液/懸濁液 #	25°C/60% RH	30°C/65% RH	40°C/75% RH
溶液 00	仕様を満たす	仕様を満たす	0.398%
溶液 02	仕様を満たす	仕様を満たす	仕様を満たす
懸濁液 01	仕様を満たす	仕様を満たす	0.289%
懸濁液 03	仕様を満たす	仕様を満たす	0.123%

【０２２８】

【表８】

表５－４：溶液００結果の概要

溶液 00, 70mg/mL, 65% ビタミンE	仕様	開始	1ヶ月 25°C/60 %RH	1ヶ月 30°C/65 %RH	1ヶ月 40°C/75 %RH	3カ月 25°C/60 %RH	3カ月 30°C/65 %RH	3カ月 40°C/75 %RH	6ヶ月 25°C/60 %RH	6ヶ月 30°C/65 %RH	6ヶ月 40°C/75 %RH
記載	黄色からオレンジの溶液	琥珀色溶液	琥珀色溶液	琥珀色溶液	琥珀色溶液	琥珀色溶液	琥珀色溶液	琥珀色溶液	琥珀色溶液	琥珀色溶液	琥珀色溶液
同定－UV	UV及びRT標品に従う	パス	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
アッセイ シアゼパム (%)	90.0から110.0%	100.1	100.3	99.9	98.8	96.3	96.9	101.2	97.5	94.6	100.6
不純物 (%) (1)											
ノルダゼパム	NMT 0.3%	0.005	0.01	0.014	0.019	0.013	0.013	0.013	0.013	0.013	0.013
関連化合物B	NMT 0.1%	ND	0.002	0.007	0.03	0.008	0.016	0.089	0.024	0.098	0.398
関連化合物A	NMT 0.01%	0.002	0.002	0.004	0.011	0.002	0.002	0.01	0.005	0.008	0.051
未知	NMT 0.1%	0.011	0.012	0.014	0.02	0.037	0.039	0.047	0.035	0.066	0.055
総計	NMT 1.0%	0.0	0.0	0.0	0.1	0.1	0.1	0.2	0.1	0.2	0.5
微生物限定	USPを満たす(61)	パス	N/A	N/A	N/A	N/A	N/A	N/A	パス	試験せず	試験せず
全重量 (g)	報告結果	1.108	1.103	1.111	1.112	1.109	1.109	1.113	1.103	1.111	1.109
全容量 (ml)	報告結果	1.192	1.189	1.195	1.196	1.193	1.193	1.198	1.187	1.195	1.193
スプレー送達 (μl)	報告結果	133.9	140.7	146.0	140.5	149.1	143.5	139.6	131.4	試験せず	136.4
平均スプレー含有量 (%)	報告結果	95.0	101.2	104.4	99.4	99.7	94.6	99.4	95.7	試験せず	103.7
粘度 (Pa*s)	報告結果	0.14	0.086	0.12	0.12	0.096	0.14	0.12	0.12	0.11	0.11

(1) LOQは約0.006%であり、LODは約0.002%である。LOQ以下の結果が、目的の方向示すためにこの表で報告される。

【０２２９】

【表９】

表５－５：溶液０２結果の概要

溶液02, 70mg/mL, 65% ビタミンE	仕様	開始	1ヶ月 25°C/60 %RH	1ヶ月 30°C/65 %RH	1ヶ月 40°C/75 %RH	3カ月 25°C/60 %RH	3カ月 30°C/65 %RH	3カ月 40°C/75 %RH	6ヶ月 25°C/60 %RH	6ヶ月 30°C/65 %RH	6ヶ月 40°C/75 %RH
記載	黄色からオレンジの溶液	琥珀色溶液	琥珀色溶液	琥珀色溶液	琥珀色溶液	琥珀色溶液	琥珀色溶液	琥珀色溶液	琥珀色溶液	琥珀色溶液	琥珀色溶液
同定－UV	UV及びRT標準品に従う	パス	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
アッセイ アセゼパム(%)	90.0から110.0%	100.5	94.9	96.2	103.3	98.0	97.2	99.6	97.0	94.3	100.3
不純物(%)(1)											
ノルダゼパム	NMT 0.3%	0.003	0.004	0.005	0.006	0.005	0.005	0.006	0.005	0.004	0.005
関連化合物B	NMT 0.1%	ND	0.002	0.003	0.006	0.003	0.005	0.032	0.007	0.020	0.058
関連化合物A	NMT 0.01%	0.003	0.002	0.002	0.003	0.002	0.002	0.004	0.003	0.009	0.007
未知	NMT 0.1%	0.01	0.012	0.014	0.018	0.019	0.025	0.032	0.014	0.020	0.018
総計	NMT 1.0%	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.1	0.1
微生物限定	USPを満たす(61)	パス	N/A	N/A	N/A	N/A	N/A	N/A	パス	試験せず	試験せず
全重量(g)	報告結果	1.135	1.117	1.128	1.123	1.116	1.133	1.137	1.124	1.133	1.127
全容量(ml)	報告結果	1.184	1.165	1.177	1.172	1.164	1.182	1.186	1.172	1.183	1.176
スプレー送達(μl)	報告結果	115.0	137.5	137.6	133.1	143.9	136.3	143.8	129.3	試験せず	124.2
平均スプレー含有量(%)	報告結果	98.6	97.6	97.7	100.7	98.7	94.7	100.5	95.8	試験せず	97.1
粘度(Pa*s)	報告結果	0.69	0.68	0.64	0.68	0.63	0.65	0.64	0.61	0.55	0.56

(1) LOQは約0.006%であり、LODは約0.002%である。LOQ以下の結果が、目的の方向示すためにこの表で報告される。

【０２３０】

【表１０】

表５－６：懸濁液０１結果の概要

懸濁液01、100 mg/ml	仕様	開始	1ヶ月 25°C/60 %RH	1ヶ月 30°C/65 %RH	1ヶ月 40°C/75 %RH	3カ月 25°C/60 %RH	3カ月 30°C/65 %RH	3カ月 40°C/75 %RH	6ヶ月 25°C/60 %RH	6ヶ月 30°C/65 %RH	6ヶ月 40°C/75 %RH
記載	濁った色から白色溶液	白色分散	白色分散	白色分散	白色分散	白色分散	白色分散	白色分散	白色分散	淡黄色分散	黄色分散
同定－UV	UV及びRT標準品に従う	パス	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
アッセイ、ジアゼパム（%）	90.0から110.0%	102.8	102.6	100.9	104.3	101.3	101.8	103.6	100.7	104.3	99.4
不純物（%）（1）											
ノルダゼパム	NMT 0.3%	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
関連化合物B	NMT 0.1%	ND	ND	ND	0.004	ND	0.004	0.053	0.005	0.013	0.289
関連化合物A	NMT 0.01%	ND	0.01	0.02	0.034	0.026	0.036	0.08	0.038	0.046	0.157
未知	NMT 0.1%	0.008	0.008	0.008	0.008	0.008	0.007	0.007	0.008	0.007	0.018
総計	NMT 1.0%	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.5
メチルパラベン（%）	80.0%-115.%	97.7	100.2	92.1	100.3	101.4	100.6	101.6	106.0	103.2	103.2
プロピルパラベン（%）	80.0%115.0%	100.2	100.5	92.2	99.2	100.6	99	100	98.5	97.6	96.7
微生物限定	USPを満たす（61）	パス	N/A	N/A	N/A	N/A	N/A	N/A	パス	試験せず	試験せず
全重量（g）	報告結果	1.254	1.252	1.252	1.244	1.246	1.248	1.247	1.245	1.242	1.235
全容量（ml）	報告結果	1.198	1.196	1.196	1.188	1.191	1.193	1.191	1.190	1.187	1.180
スプレー送達（μl）	報告結果	132.5	131.2	126	123.9	137.6	137.8	136.3	140.0	試験せず	137.6
平均スプレー含有量（%）	報告結果	92.2	94.2	91.1	89.9	101.5	100.4	95.3	101.8	試験せず	95.94
粘度（Pa*s）	報告結果	0.0098	0.0098	0.0092	0.0090	0.0092	0.0093	0.0089	0.0082	0.0080	0.0092

（１）LOQは約0.006%であり、LODは約0.002%である。LOQ以下の結果が、目的の方向示すためにこの表で報告される。

【０２３１】

【表１１】

表５－７：懸濁液Ｏ３結果の概要

懸濁液03、200mg/mL	仕様	開始	1ヶ月 25℃/60%RH	1ヶ月 30℃/65%RH	1ヶ月 40℃/75%RH	3カ月 25℃/60%RH	3カ月 30℃/65%RH	3カ月 40℃/75%RH	6ヶ月 25℃/60%RH	6ヶ月 30℃/65%RH	6ヶ月 40℃/75%RH
記載	薄ら白色から白色分散	白色分散	白色分散	白色分散	白色分散	白色分散	白色分散	白色分散	白色分散	淡黄色分散	黄色分散
同定－UV	UV及びRT標準品に従う	パス	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
アッセイ シアゼパム（%）	90.0から110.0%	100.7	101.2	98.9	101.6	102.6	103.6	103.1	100.5	98.9	100.1
不純物（%）（1）											
ノルダゼパム	NMT 0.3%	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
関連化合物B	NMT 0.1%	ND	ND	ND	ND	0.002	ND	0.023	0.002	0.008	0.123
関連化合物A	NMT 0.01%	ND	0.005	0.01	0.017	0.017	0.012	0.039	0.019	0.029	0.081
未知	NMT 0.1%	0.008	0.008	0.008	0.008	0.008	0.008	0.006	0.008	0.007	0.008
総計	NMT 1.0%	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.2
メチルパラベン（%）	80.0%-115.%	93.4	101.1	93.8	99.7	101.5	101.6	101.2	103.5	97.2	102.1
プロピルパラベン（%）	80.0%115.0%	95.6	100.2	94	98.4	100.1	101.3	99.2	97.1	91.9	95.9
微生物限定	USPを満たす{61}	パス	N/A	N/A	N/A	N/A	N/A	N/A	パス	試験せず	試験せず
全重量（g）	報告結果	1.276	1.28	1.259	1.272	1.279	1.279	1.276	1.280	1.262	1.260
全容量（ml）	報告結果	1.186	1.19	1.171	1.183	1.19	1.19	1.187	1.190	1.173	1.172
スプレー送達（μl）	報告結果	112.4	137.4	134.3	119.9	138.9	139.3	134.3	149.4	試験せず	138.0
平均スプレー含有量（%）	報告結果	82.8	99.3	97.3	86.7	98.6	102.3	96.2	98.2	試験せず	98.7
粘度（Pa*s）	報告結果	0.021	0.017	0.017	0.019	0.016	0.016	0.018	0.014	0.013	0.015

（1）LOQは約0.006%であり、LODは約0.002%である。LOQ以下の結果が、目的の方向示すためにこの表で報告される。

【０２３２】

【表１２】

表5-8: 溶液00 25℃/60%RH スプレー内容物均一性結果

サンプル	収集重量, g	作動重量, g	回収ジアゼパム, mg	% 回収ジアゼパム
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
平均	0.13135	0.13716	9.380	95.72
標準偏差	0.0070	0.0071	0.4309	4.3970
% RSD	5.35	5.20	4.59	4.59

【０２３３】

【表１３】

表5-9: 溶液00 40℃/75%RH スプレー内容物均一性結果

サンプル	収集重量, g	作動重量, g	回収ジアゼパム, mg	% 回収ジアゼパム
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
平均	0.13635	0.14131	10.653	108.70
標準偏差	0.0097	0.0095	0.8884	9.0649
% RSD	7.14	6.76	8.34	8.34

【０２３４】

【表１４】

表5-10: 溶液02 25℃/60%RH スプレー内容物均一性結果

サンプル	収集重量, mg	作動重量, mg	回収 ジアゼパム, mg	% 回収 ジアゼパム
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
平均	0.12931	0.13178	9.394	95.85
標準偏差	0.0058	0.0056	0.3303	3.3701
%RSD	4.52	4.25	3.52	3.52

【０２３５】

【表１５】

表5-11: 溶液02 40℃/75%RH スプレー内容物均一性結果

サンプル	収集重量, g	作動重量, g	回収 ジアゼパム, mg	% 回収 ジアゼパム
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
平均	0.12423	0.12649	9.517	97.11
標準偏差	0.0254	0.0260	0.3148	3.2119
%RSD	20.45	20.57	3.31	3.31

【０２３６】

【表１６】

表5-12:懸濁液01 25℃/60%RH スプレー内容物均一性結果

サンプル	収集重量, g	作動重量, g	回収 ジアゼパム, mg	% 回収 ジアゼパム
1	0.12873	0.12999	12.85366	91.81
2	0.14011	0.14247	13.68122	97.72
3	0.14515	0.14757	14.09449	100.67
4	0.13205	0.13347	14.18775	101.34
5	0.14554	0.14743	14.48202	103.44
6	0.14473	0.14682	14.39897	102.85
7	0.13229	0.13411	14.87853	106.28
8	0.14357	0.14581	14.82712	105.91
9	0.14741	0.14940	14.86732	106.20
平均	0.13995	0.14190	14.252	101.80
標準偏差	0.0070	0.0074	0.6602	4.7154
%RSD	5.03	5.18	4.63	4.63

【０２３７】

【表１７】

表5-13: 懸濁液01 40℃/75%RH スプレー内容物均一性結果

サンプル	収集重量, g	作動重量, g	回収 ジアゼパム, mg	% 回収 ジアゼパム
1	0.14411	0.14869	13.04770	93.20
2	0.14066	0.14151	13.23277	94.52
3	0.13012	0.13485	13.78126	98.44
4	0.14667	0.14879	13.36970	95.50
5	0.14294	0.14338	12.54309	89.59
6	0.13797	0.14253	13.25396	94.67
7	0.13374	0.13594	13.41984	95.86
8	0.12388	0.12559	14.34944	102.50
9	0.13790	0.14011	13.88564	99.18
平均	0.13755	0.14015	13.431	95.94
標準偏差	0.0073	0.0073	0.5223	3.7310
%RSD	5.28	5.19	3.89	3.89

【０２３８】

【表１８】

表5-14: 懸濁液03 25℃/60%RH スプレー内容物均一性結果

サンプル	収集重量, g	作動重量, g	回収ジアゼパム, mg	% 回収ジアゼパム
1	0.13604	0.13897	25.93418	92.62
2	0.14608	0.14792	26.21721	93.63
3	0.15294	0.15425	30.05570	107.34
4	0.14728	0.14910	25.78804	92.10
5	0.15352	0.15493	26.60721	95.03
6	0.15242	0.15401	29.51030	105.39
7	0.15118	0.15254	28.43104	101.54
8	0.15322	0.15556	28.03664	100.13
9	0.15197	0.15393	26.82906	95.82
平均	0.14941	0.15125	27.490	98.18
標準偏差	0.0057	0.0053	1.5812	5.6472
%RSD	3.79	3.50	5.75	5.75

【０２３９】

【表１９】

表5-15: 懸濁液03 40℃/75%RH スプレー内容物均一性結果

サンプル	収集重量, g	作動重量, g	回収ジアゼパム, mg	% 回収ジアゼパム
1	0.13574	0.13797	28.14588	100.52
2	0.13639	0.13803	27.04437	96.59
3	0.14082	0.14195	26.78985	95.68
4	0.12962	0.13249	29.07192	103.83
5	0.12518	0.12683	27.39785	97.85
6	0.14423	0.14541	28.50133	101.79
7	0.13922	0.14096	27.34617	97.66
8	0.14146	0.14313	27.17415	97.05
9	0.14902	0.15344	27.20939	97.18
平均	0.13796	0.14002	27.631	98.68
標準偏差	0.0073	0.0076	0.7642	2.7294
%RSD	5.28	5.43	2.77	2.77

【０２４０】

実施例６

実施例３及び４に記載される溶液及び懸濁液の全ては、本明細書中に記載される追加の適当量のアルキルグリコシド、例えば、ドデシルマルトシド、テトラデシルマルトシド、スクロースドデカノエイト、スクロースモノステアリン、スクロースジステアリン、及び／又は２又はそれより多いそれらの組合せ、あるいはＡｅｇｉｓ Ｔｅｒａｐｅｕｔｉｃｓ，サンディエゴ、カリホルニアにより市販されているＩｎｔｒａｖａｉｌ（登録商標）

等と共に製剤される。添加されたアルキルグリコシドを備える溶液及び懸濁液は、変更すべきところは変更して、実施例５に記載されるように安定性を加える。

【０２４１】

実施例７

実施例３、４及び６の溶液及び懸濁液は、適切な動物モデル例えば、マウス、ラット、ウサギ又は犬等で薬物動態を評価される。先ず、夫々の動物（例えば、ウサギ）がベンゾジアゼピン薬の量を静脈内投与される。静脈内投与されたベンゾジアゼピン薬の量は、より少ない量が選択され、例えば、鼻腔内投与に効果的な投与量と判断される量のおおよそ半分が選択される。例えば、ウサギに投与されるジアゼパムの静脈内投与量は、約０．０５から０．２ｍｇ／ｋｇ、例えば、約０．１ｍｇ／ｋｇである。投与前及び投与後特定時間で血液が直ちに採血される。血漿中の薬物レベルが、夫々の血液サンプルでアッセイされる。少なくとも１日の休薬期間の後、夫々の動物は、実施例３、４及び６に記載される溶液又は懸濁液の量を静脈内に投与される。血液は、投与前及び静脈内投与後と略同じ特定時間に、直ちに採血された。薬物動態曲線は（時間に対する薬物の血漿中濃度）、投与の静注経路で構成されるとともに、鼻腔内投与経路で投与される溶液及び懸濁液の夫々で構成される。

【０２４２】

毒性は、既知の方法により評価される。特に、組織学的試料は、試験動物の鼻粘膜組織から採取される。他の毒物学的方法が同様に任意に用いられる。

【０２４３】

実施例８

実施例３、４及び６の溶液及び懸濁液は、適切な動物モデル例えば、マウス、ラット、ウサギ又は犬等での血液脳関門を越えて薬物を送達する能力が評価される。夫々の動物は、血液脳関門を通過する薬物の能力を決定するために、代用品として使用される造影剤例えば色素を任意に含む溶液又は懸濁液で、実施例３、４及び６に記載の溶液又は懸濁液の量を鼻腔内に投与される。薬物又は造影剤がどのように血液脳関門を通過するのかを決定するために、懸濁液又は溶液の投与後、溶液又は造影剤が選択時間点で検出される。これらの結果は、薬物又は造影剤を含む静脈注射用の溶液で得られた類似の結果と比較された。

【０２４４】

実施例９

上記の溶液及び／又は懸濁液は、ヒトにおける薬物動態で評価され得る。通常、健康なヒト被験者は、薬物の量を静脈内投与される。静脈内投与に選択される量は、任意の量であるが、人の発作を処置するのに効果的と考えられるに都合のよい投与量である。ヒトに投与されるジアゼピンの静脈内投与は、１から１５ｍｇの範囲であり、例えば約７．５ｍｇである。血液は、投与前及び投与後の選択時間点で直ちに採血される。薬物の血漿中濃度が、血液試料の夫々でアッセイされる。少なくとも１日の休薬期間の後、夫々の被験者は、本明細書中に記載される溶液又は懸濁液の量を、静脈内に投与される。血液は、投与前及び静脈内投与後の略同じ特定時間に、直ちに採血される。静脈注射時点と略同じ投与後時点で直ちに採血される。薬物動態曲線は（時間に対する薬物の血漿中濃度）、静脈投与経路及び鼻腔内投与経路で構成される。

【０２４５】

実施例１０

上記溶液及び／又は懸濁液は、適切な動物モデルで有効性が評価される。手短に言うと、試験される溶液又は懸濁液の各投与量に対して、試験動物が、発作誘発刺激で刺激される。刺激は、光刺激、音刺激、化学刺激又は他の刺激であり、効果的にモデル動物において発作を誘導する。動物は、発病するとすぐに、本明細書中に記載される溶液又は懸濁液が、動物に鼻腔内投与される。溶液及び／又は懸濁液の投与量の有効性は、試験投与量に対する動物の反応に基づいて評価される。この手段は、十分量の反復を介して繰り返され、十分な数の投与で繰り返され、薬物の鼻腔内投与により発作を処置するに効果的と考え

られる投与量が確認される。

【０２４６】

本発明の好適な実施形態は、本明細書中に示され、記載されているが、このような実施形態が、限定されることなく提供されることは、当該分野の当業者にとって明らかである。多くの変化、変更、及び置換は、本発明から逸脱することなく、当該分野の当業者に思い浮かぶだろう。本明細書中に記載される本発明の実施形態の様々な代替は、本発明を実行するのに使用されることを理解されるべきである。次の請求項は、本発明の範囲、これら請求項の範囲内の方法及び構造を規定し、それら等価物はそれらによりカバーされることを目的とする。

【国際調査報告】

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2009/038696

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/5513(2006.01)i, A61K 31/355(2006.01)i, A61K 9/16(2006.01)i, A61K 47/10(2006.01)i, A61P 25/22(2006.01)i

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)
IPC8 as above

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS, Google scholar

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2007043057 A2 (TOUITOU, ELKA et. al.) 19 April 2007 See claims 18 and 35, p. 6 (line 1-3), 8 (line 3-11)	1-19
A	WO 2005117830 A1 (CAMURUS AB, SWED) 15 December 2005 See whole document	1-19
A	WO 2006075123 A1 (CAMURUS AB, SWED) 20 July 2006 See whole document	1-19
A	WO 2007144081 A2 (LTS LOHMANN THERAPIE-SYSTEM A.-G.) 21 December 2007 See whole document ----------//	1-19

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* 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 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
28 SEPTEMBER 2009 (28.09.2009)	**28 SEPTEMBER 2009 (28.09.2009)**
Name and mailing address of the ISA/KR Korean Intellectual Property Office Government Complex-Daejeon, 139 Seonsa-ro, Seo-gu, Daejeon 302-701, Republic of Korea Facsimile No. 82-42-472-7140	Authorized officer KIM, YONG Telephone No. 82-42-481-8164

Form PCT/ISA/210 (second sheet) (July 2008)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2009/038696

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.: 20-45
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 20-45 pertain to methods for treatment of the human body by therapy, as well as prevention method, and thus relate to a subject matter which this International Searching Authority is not required, under Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT, to search.

2. ☒ Claims Nos.: 46, 47
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:
Claims 46 and 47 relate to a composition, and are indicated as referring to claims 20 and 21, respectively. However, the claims 20 and 21 relate to a method of treating a patient. Thus claims 46 and 47 are too unclear to make meaningful search possible

3. ☐ Claims Nos.:
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 an additional fee, this Authority did not invite payment of any additional fee.

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.

Form PCT/ISA/210 (continuation of first sheet (2)) (July 2008)

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/US2009/038696

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007-043057 A2	19.04.2007	CN 101325944 A	17.12.2008
		EP 1933809 A2	25.06.2008
		JP 2009-511571 A	19.03.2009
		WO 2007-043057 A3	15.11.2007
		WO 2007-043057 A3	19.04.2007
WO 2005-117830 A1	15.12.2005	AT 401054 T	15.08.2008
		AU 2005-249274 A1	06.06.2005
		AU 2005-324794 A1	09.12.2005
		PI 0511807 A	15.01.2008
		CA 2569513 A1	15.12.2005
		CA 2594710 A1	20.07.2006
		CA 2594718 A1	20.07.2006
		CA 2594711 A1	20.07.2006
		CA 2609810 A1	14.12.2006
		CN 101217940 A	09.07.2008
		CN 101217940 A0	09.07.2008
		DE 602005008247 D1	28.08.2008
		DK 1768650 T3	29.09.2008
		EP 1848403 A1	31.10.2007
		EP 1845942 A1	24.10.2007
		EP 1843746 A1	17.10.2007
		EP 1768650 B1	16.07.2008
		EP 1768650 A1	04.04.2007
		EP 1888031 A1	20.02.2008
		ES 2309766 T3	16.12.2008
		JP 2008-501676 T	24.01.2008
		JP 2008-526932 A	24.07.2008
		JP 2008-501676 A	24.01.2008
		JP 2008-526933 A	24.07.2008
		JP 2008-542437 A	27.11.2008
		JP 2008-526934 A	24.07.2008
		KR 10-2007-0046815 A	03.05.2007
		KR 10-2007-0104599 A	26.10.2007
		US 2009-0170782 A1	02.07.2009
		US 2009-0155193 A1	18.06.2009
		US 2009-0069221 A1	12.03.2009
		US 2008-0146490 A1	19.06.2008
		US 2008-0124394 A1	29.05.2008
		US 2007-0265190 A1	15.11.2007
		US 2008-0085263 A1	10.04.2008
		WO 2006-075123 A1	20.07.2006
		WO 2006-075125 A1	20.07.2006
		WO 2006-075124 A1	20.07.2006
		WO 2006-131730 A1	14.12.2006

(Continued on Next Page)

Form PCT/ISA/210 (patent family annex) (July 2008)

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/US2009/038696

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006-075123 A1	20.07.2006	AU 2005-249274 A1	06.06.2005
		AU 2005-324794 A1	09.12.2005
		CA 2569513 A1	15.12.2005
		CA 2594710 A1	20.07.2006
		CA 2594711 A1	20.07.2006
		CA 2594718 A1	20.07.2006
		CA 2609810 A1	14.12.2006
		CN 101217940 A	09.07.2008
		CN 101217940 A0	09.07.2008
		EP 1848403 A1	31.10.2007
		EP 1845942 A1	24.10.2007
		EP 1843746 A1	17.10.2007
		EP 1768650 B1	16.07.2008
		EP 1768650 A1	04.04.2007
		EP 1888031 A1	20.02.2008
		JP 2008-542437 A	27.11.2008
		JP 2008-526934 A	24.07.2008
		JP 2008-526933 A	24.07.2008
		JP 2008-526932 A	24.07.2008
		JP 2008-501676 A	24.01.2008
		KR 10-2007-0046815 A	03.05.2007
		KR 10-2007-0104599 A	26.10.2007
		US 2007-0265190 A1	15.11.2007
		US 2008-0085263 A1	10.04.2008
		US 2009-0170782 A1	02.07.2009
		US 2009-0155193 A1	18.06.2009
		US 2009-0069221 A1	12.03.2009
		US 2008-0146490 A1	19.06.2008
		US 2008-0124394 A1	29.05.2008
		WO 2006-075125 A1	20.07.2006
		WO 2006-075124 A1	20.07.2006
		WO 2005-117830 A1	15.12.2005
		WO 2006-131730 A1	14.12.2006
WO 2007-144081 A2	21.12.2007	CA 2654477 A1	21.12.2007
		DE 102006027795 A1	20.12.2007
		EP 2029098 A2	04.03.2009
		WO 2007-144081 A3	10.04.2008
		WO 2007-144081 A3	21.12.2007

Form PCT/ISA/210 (patent family annex) (July 2008)

フロントページの続き

(51)Int.Cl.			F I		テーマコード（参考）
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A61K	***9/12***	***(2006.01)***	A61K	9/12	
A61K	***9/08***	***(2006.01)***	A61K	9/08	
A61K	***9/10***	***(2006.01)***	A61K	9/10	
A61P	***25/08***	***(2006.01)***	A61P	25/08	

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(54) Title: OIL-IN-WATER EMULSIONS COMPRISING A BENZODIAZEPINE DRUG

(57) Abstract: There is provided oil-in-water emulsion compositions comprising a benzodiazepine drug, such as midazolam, that is dissolved in an oil phase that comprises 1 to 35% (w/w) vitamin E.

OIL-IN-WATER EMULSIONS COMPRISING A BENZODIAZEPINE DRUG

This invention relates to new oil-in-water emulsion compositions.

Emulsion systems have long been used for pharmaceutical purposes. Such systems include oil-in-water emulsions, water-in-oil emulsions and more complex systems known as multiple emulsions.

Oil-in-water emulsions, in which the continuous phase is aqueous and the dispersed phase is oily in nature, may be used for a variety of purposes and administered *via* a variety of routes, including injection as well as administration to the eye, nose, lung, gastrointestinal tract or vagina.

Benzodiazepine compounds, which act on the central nervous system to cause sedation, hypnosis, decreased anxiety, muscle relaxation, anterograde amnesia and to prevent convulsions, are widely used in medicine. The benzodiazepine drug midazolam (8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5α-][1,4]benzodiazepine) is used as a sedative, especially in a hospital setting and particularly as premedication prior to surgery.

The intranasal administration of aqueous solutions of midazolam as a sedative prior to minor invasive surgical and medical procedures has been widely reported (see, for example, S. Björkman *et al. British Journal of Anaesthesia* 79, 575-580 (1997) and N. C. T. Wilton *et al. Anesthesiology* 69, 972-975 (1988)). It has been especially used in the paediatric patient group. Apart from being a patient group in which alleviation of anxiety is particularly beneficial, the use of intranasal midazolam has been largely confined to children because of limited solubility of the drug substance. The aqueous solubility of midazolam is low, and to deliver a therapeutic dose to an adult by the intranasal route would require a prohibitively large

dose volume. An additional drawback of the intranasal administration of midazolam, and which could limit its use (especially in children), is the irritation and stinging that it causes in the nasal cavity. At least part of the cause of this discomfort is thought to be the acidic pH of the simple aqueous solutions of midazolam that are used.

WO 00/24373 describes oil-in-water emulsions of drugs that are poorly soluble in water, especially non-steroidal anti-inflammatory drugs and drugs for the treatment of pain, erectile dysfunction and Parkinson's disease. Compositions comprising Vitamin E and benzodiazepines are neither disclosed nor suggested.

Compositions comprising benzodiazepines are described in US 4,950,664. The use of vitamin E in such compositions is neither disclosed nor suggested. Further, preferred dosage forms are solutions, suspensions and gels.

A formulation containing 17 mg/mL midazolam, achieved by using sulfobutylether-β-cyclodextrin as a solubilising agent, has been described by Loftsson *et al.* (*Int. J. Pharm.* 212, 29-40, (2001)). Penkler et al describes the use of randomly methylated β-cyclodextrin to produce a solution containing 10 mg/mL midazolam (*AAPS PharmSci. Supplement* 1, S-3642, (1999)).

WO 97/03651 describes emulsion compositions containing vitamin E as a solubilising agent. There is no suggestion in this document of emulsions containing benzodiazepines.

Emulsion formulations of drug compounds are described in US 6,193,985. The compositions comprise active agent dissolved in an oil phase comprising tocopherol (vitamin E), wherein the vitamin E comprises 20 to 95% w/w of the compositions. The second phase of the emulsion comprises vitamin E TPGS as the emulsifying agent. Vitamin E TPGS is a water soluble derivative of vitamin E and consists of tocopherol esterified with succinic acid, the other acidic group of the latter being esterified with polyethylene glycol 1000. Compositions in which the oil phase comprises 1 to 35% (w/w) of vitamin E are neither disclosed nor suggested.

Nonetheless, there is an unmet need for benzodiazepine (and especially midazolam) compositions that contain high concentrations of active agent, that give minimal irritation of the nasal cavity on intranasal administration, and that are stable over prolonged periods.

We have found, surprisingly, that the above-mentioned problems may be solved using an emulsion formulation in which both the amount of oil phase in the emulsion as well as the vitamin E content of that oil phase are carefully selected. We have additionally found that emulsion stability may be further enhanced by addition of a non-ionic surfactant and/or a cellulose-based thickening agent. When administered into the nasal cavity, the emulsion is well tolerated.

Thus, according to the invention there is provided oil-in-water emulsion compositions for the delivery of a benzodiazepine drug to a patient comprising:

(a) an oil phase, which phase comprises 10 to 60% (w/v) of the emulsion, and which phase comprises vitamin E in an amount 1 to 35% (w/w of that phase) and a benzodiazepine drug;

(b) an aqueous phase; and

(c) an emulsion stabiliser,

which compositions are referred to hereinafter as "the emulsions according to the invention".

It is preferred that the emulsions according to the invention are adapted for intranasal administration.

When used herein, the term "vitamin E" includes all tocol and tocotrienol derivatives that exhibit vitamin E activity. It is preferred that the vitamin E is water insoluble and/or non-water dispersible. The nomenclature for vitamin E and related compounds is unclear in current practice and can vary when used by different compendia and organisations. The United States Pharmacopoeia describes vitamin E as a form of α-tocopherol. This includes D- or D,L-α-tocopherol, D- or D,L-α-tocopherol acetate and D- or D,L-α-tocopherol succinate. The Association of Official Analytical Chemists (AOAC) states that the term vitamin E should be used as a generic description for all tocol and tocotrienol derivatives that exhibit vitamin E activity. Thus the term tocopherols is synonymous with vitamin E but also for methyl tocols. α-Tocopherol is a trivial name without defined stereochemistry.

The vitamin E is preferably in the form of the free alcohol, but suitable tocopherol derivatives include esters of tocopherol such as the linoleate, nicotinate, acetate or acid succinate ester.

The emulsions according to the invention have an oil phase that comprises one or more pharmaceutically acceptable oils. These oils are preferably non-hydroxylated (i.e. they have a hydroxyl value of less than 20) and as such they include vegetable oils such as soybean oil, sesame oil, safflower

oil, canola oil, corn oil, cottonseed oil and olive oil as well as marine oils such as cod liver oil and sardine oil. Preferred oils are sesame oil, canola oil, corn oil, cottonseed oil, and, especially, soybean oil.

The emulsions according to the invention preferably have an oil phase that represents 12 to 50% (w/v) and more preferably 15 to 40% (w/v) of the total emulsion. Further, the emulsions according to the invention preferably have an oil phase that comprises 2.5 to 30% (w/w) (such as 5 to 25% (w/w)) vitamin E.

When used herein, the term "benzodiazepine drug" will be understood by those skilled in the art to include all pharmacologically active compounds that possess the benzodiazepine (sub-)structure, and which may act on the central nervous system. See also the definition provided in Goodman & Gilman's "*The Pharmacological Basis of Therapeutics*", 9th Edition (1996), McGraw-Hill at pages 363 and 364, the relevant disclosure in which document is hereby incorporated by reference. Examples of suitable benzodiazepine drugs include alprazolam, bentazepam, bromazepam, brotizolam, camazepam, chlordiazepoxide, cinolazepam, clobazam, clonazepam, clorazepic acid, clorazepate, clotiazepam, clozapine, delorazepam, diazepam, estazolam, ethyl loflazepate, etizolam, fludiazepam, flunitrazepam, flurazepam, halazepam, ketazolam, loprazolam, lorazepam, lormetazepam, metaclazepam, mexazolam, midazolam, nimetazepam, nitrazepam, oxazepam, pinazepam, prazepam, quazepam, temazapem, tetrazepam and triazolam. Preferred benzodiazepine drugs include alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, estazolam, flurazepam, halazepam, lorazepam, nitrazepam, oxazepam, prazepam, quazepam, temazapem, triazolam and, especially, midazolam.

The benzodiazepine drug content of the emulsions according to the invention is dependent upon the solubility of the benzodiazepine drug in question and the dose that needs to be delivered to the patient. For an intranasal formulation delivered as a liquid, the typical dose volume is in the range 0.1 to 0.4 mL although smaller or larger volumes may also be given. The benzodiazepine drug may be incorporated into the emulsions according to the invention by being dissolved into the oil phase prior to emulsification. The benzodiazepine drug content of the oil phase prior to preparation of the emulsions according to the invention is preferably in the range 1 to 1000 mg/mL, more preferably 2 to 800 mg/mL and most preferably 4 to 600 mg/mL. The benzodiazepine drug content of the final oil-in-water emulsion is preferably in the range 0.1 to 300 mg/mL, more preferably 0.5 to 250 mg/mL and most preferably 1 to 200 mg/mL.

When used herein, the term "emulsion stabiliser" refers to agents that, when present in emulsions according to the invention, either prevent or retard phase separation (i.e. the formation of distinct oil and/or water layers) in the emulsions. The term therefore includes agents that prevent phase separation in the emulsions according to the invention for one or more hours or, preferably, for one or more days (e.g. 3 or more days, such as one or more weeks, and, particularly, one or more months).

The emulsion stabiliser is preferably incorporated into the emulsions according to the invention *via* the aqueous phase. Preferred emulsion stabilisers include one or more thickening and/or, particularly, emulsifying agents. Suitable thickening agents include cellulose-based thickening agents such as methylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose and hydroxypropyl methylcellulose. Suitable emulsifying agents include:

(a) ionic surfactants (e.g. phospholipids such as lecithin); and

(b) non-ionic surfactants (e.g. polyoxyethylene sorbitan fatty acid esters, polyoxyethylene stearates, polyoxyethylene castor oil derivatives and polyoxyethylene alkyl ethers).

Detailed descriptions of the non-ionic surfactants mentioned above may be found in the "*Handbook of Pharmaceutical Excipients*", Kibbe (ed), 3rd edition, American Pharmaceutical Association (Washington) and Pharmaceutical Press (London), 2000.

Principle sources of lecithin are eggs and soybeans. Synonyms for lecithin include egg lecithin; mixed soybean phosphatides; ovolecithin; egg yolk phospholipids; soybean lecithin; soybean phospholipids; vegetable lecithin.

Preferred emulsions according to the invention include those that include an emulsion stabiliser that is an emulsifying agent (e.g. an ionic surfactant such as lecithin). In this respect, preferred emulsions according to the invention also include those in which lecithin is employed as an emulsion stabiliser, and a non-ionic surfactant and/or a thickening agent, as hereinbefore defined, is/are optionally employed as (a) further emulsion stabiliser(s).

The amount of emulsion stabiliser (e.g. lecithin) used in the emulsion according to the invention is preferably in the range 0.01 to 15% (w/v), more preferably 0.05 to 10% (w/v) and most preferably 0.1 to 5% (w/v).

When present in the emulsions according to the invention, the non-ionic surfactant may have a concentration that is preferably in the range 0.01 to 25% (w/v), more preferably 0.05 to 20% (w/v) and most preferably 0.1 to 15% (w/v).

When present in the emulsions according to the invention, the thickening agent may have a concentration that is dependent upon its molecular weight. However, its concentration in an emulsion according to the invention is preferably in the range 0.01 to 20% (w/v), more preferably 0.05 to 15% (w/v) and most preferably 0.1 to 10% (w/v).

The pH of the emulsions according to the invention is an important determinant of how well they are tolerated when administered into the nasal cavity. The emulsion may cause irritation and stinging if the pH is too high or low. Further, when the emulsion according to the invention comprises midazolam, it is also preferable to avoid a low pH in order to minimise drug partitioning from the oil phase into the aqueous phase. High concentrations of midazolam in the aqueous phase may exacerbate irritation.

Measuring accurately the pH of an oil-in-water emulsion may be problematic. Indeed, it may be more convenient to measure the pH of the aqueous phase of the emulsion. This measurement may be performed by centrifugation of the emulsion at a force adequate to separate the oil and aqueous phases into separate layers. The aqueous layer may then be removed and the pH measured. The pH of the aqueous phase of an emulsion according to the invention is preferably in the range pH 5.0 to 8.0, more preferably 5.25 to 7.8 and most preferably pH 5.5 to 7.6.

The pH of the aqueous phase of the emulsions according to the invention may be adjusted and controlled by means well known to those skilled in the art, such as buffer salts, acids and bases. Thus, the aqueous phase may contain one or more of the following pH controlling agents: organic acids (e.g. citric acid and the like) or alkali metal (e.g. sodium) salts thereof, pharmaceutically acceptable salts (e.g. sodium, magnesium or calcium salts) of inorganic acids (such as carbonic acid or phosphoric acid), oxides of

magnesium, as well as alkali, and alkaline earth, metal (e.g. sodium, calcium, potassium and the like) sulphates, metabisulphates, propionates and sorbates. The aqueous phase may, in particular, comprise a buffered aqueous solution, such as phosphate-buffered saline, that has a pH within any of the above-mentioned ranges (e.g. pH 7.4).

The emulsions according to the invention may, if necessary, be adjusted to approximately the same osmotic pressure as that of the body fluids. This may be desirable where a composition is to be applied to delicate tissue membranes, such as those found in the nasal cavity. A composition that has been adjusted in this manner is said to be isotonic and will not tend to swell or contract the tissues with which it comes into contact and will result in minimal discomfort on application. The formation of isotonic preparations may be achieved by adding an ionic compound, such as sodium chloride, or a non-ionic compound to the composition. Suitable non-ionic compounds include glycerol and mannitol.

The emulsions according to the invention may also contain other ingredients in the oil and/or aqueous phases such as antioxidants, chelating agents, preservatives or other agents generally used in pharmaceutical liquid or emulsion formulations. Such agents are well known to those skilled in the art.

Preferred emulsions according to the invention include those that are stable with respect to phase separation for one or more days (e.g. 3 or more days, such as one or more weeks, and, particularly, one or more months). When used herein, the term "stable with respect to phase separation" includes compositions that, on storage, either do not form a distinct oil layer or form a distinct layer of non-coalesced oil droplets that may be redispersed by

gentle shaking (e.g. shaking by hand) alone. The latter process, by which a layer of stabilised oil droplets separates, is known as "creaming".

In their simplest form, the emulsions according to the invention are prepared by dissolving or dispersing emulsion stabiliser in the aqueous phase. The aqueous phase is then mixed with the oil phase (comprising vitamin E, oil and the benzodiazepine drug) to form a dispersion of oil droplets.

Thus, according to a further aspect of the invention, there is provided a process for the preparation of an emulsion according to the invention, which process comprises:

(i) addition of an emulsion stabiliser, as hereinbefore defined, to an aqueous component (e.g. water) to form the aqueous phase;

(ii) addition of vitamin E, and of a benzodiazepine drug, as hereinbefore defined, to an oil to form the oil phase; and

(iii) mixing the oil phase and the aqueous phase together.

The size and size distribution of the oil droplets in the emulsions according to the invention will depend on the method of mixing. In stable emulsions, the droplet size, as measured by techniques such as light microscopy or laser diffraction, generally lies in the range 0.1 to 10 μm. High shear mixing using equipment such as a homogeniser or a microfluidiser is the preferred method of preparing pharmaceutical emulsions.

According to a further aspect of the invention, there is provided the use of an emulsion according to the invention for the manufacture of a medicament for the administration of a benzodiazepine drug (e.g. midazolam) to a patient in need of such administration.

Similarly, another aspect of the invention provides a method of administering a benzodiazepine drug (e.g. midazolam) to a patient, which method comprises administering to the patient an emulsion according to the invention.

In another aspect of the invention, there is provided the use of an emulsion according to the invention in the manufacture of a medicament for the treatment of a condition in which benzodiazepine drug treatment is indicated.

Particular conditions where benzodiazepine drug treatment may be indicated include anxiety disorders, convulsive disorders (e.g. febrile convulsions and convulsions from status epilepticus), disturbed behaviour, parasomnias (e.g. insomnia, restless leg syndrome, sleepwalking or night terrors), dyspnoea, muscle spasm (e.g. from spasticity, dystonias, stiff-man syndrome, cerebral palsy, poisoning or tetanus), emesis (e.g. nausea and vomiting associated with, for example, cancer chemotherapy), schizophrenia, vertigo and withdrawal syndromes (e.g. alcohol or opioid withdrawal).

Benzodiazepine drugs may also be given for premedication (e.g. before general anaesthesia or to provide sedative cover for minor surgical or investigative procedures) and/or to induce sedation, hypnosis and/or anterograde amnesia. Preferred indications include the provision of sedative cover for minor surgical or investigative procedures.

The emulsions according to the invention may be administered orally or parenterally. When used herein, the term "parenterally" includes administration to the muscles, subcutaneous tissue, peritoneal cavity, venous system, arterial system, lymphatic system, spinal fluid (intrathecal,

epidural) and joint cavities. Parenteral formulations will be sterile and usually pyrogen-free.

The emulsions according to the invention may also be administered to the gastrointestinal tract or other mucosal surfaces, such as the eye, nose, vagina or rectal cavity.

It is preferred that the emulsions according to the invention are administered intranasally. When adapted for intranasal administration, the emulsions according to the invention may be administered to the nasal cavity in forms including drops or sprays. Spray devices can be single ("unit") dose or multiple dose systems and are available from various commercial sources, including Pfeiffer, Valois, Bespak and Becton-Dickinson.

Emulsions according to the invention have the advantage that they may be more stable than (particularly with respect to phase separation), be better tolerated than, be less toxic than, have fewer side effects than, have better pharmacokinetic properties than, be more easily prepared than, or have any other useful properties over, compositions known in the prior art.

Moreover, emulsions according to the invention also have the advantage that they may be prepared using established pharmaceutical processing methods and employ materials that are approved for use in food or pharmaceuticals or are of like regulatory status.

The invention is illustrated, but in no way limited, by the following examples.

Examples

Example 1

Placebo emulsion comprising 25% w/v oil phase in which oil phase comprises 40% w/w vitamin E

The oil phase was prepared by mixing 10 g of vitamin E (Sigma, Poole, UK) with 15 g of soybean oil (Oleificio SABO, Manno, Switzerland). Into 50 mL of phosphate buffered saline solution (PBS; Sigma) was dispersed 1.2 g of egg yolk phospholipid (lecithin; Kabi Pharmacia, Sweden), followed by the addition of 2.2 g of glycerol (Sigma). A coarse emulsion was prepared by mixing the oil and aqueous phases using a Silverson L4R homogeniser. The coarse emulsion was adjusted to a 100 mL volume with PBS and further emulsified by passing through a Rannie Mini-Lab high pressure valve homogeniser set at 1000 bar pressure.

Example 2

Placebo emulsion comprising 25% w/v oil phase in which oil phase comprises 20% w/w vitamin E

The oil phase was prepared by mixing 5 g of vitamin E with 20 g of soybean oil. The emulsion was then prepared in an identical manner to Example 1.

Example 3

Placebo emulsion comprising 33.3% w/v oil phase in which oil phase comprises 20% w/w vitamin E

The oil phase was prepared by mixing 6.66 g of vitamin E with 26.64 g of soybean oil. The emulsion was then prepared in an identical manner to Example 1.

Example 4

Placebo emulsion comprising 40% w/v oil phase in which oil phase comprises 20% w/w vitamin E

The oil phase was prepared by mixing 8 g of vitamin E with 32 g of soybean oil. The emulsion was then prepared in an identical manner to Example 1.

Example 5

Stability of emulsions prepared in Examples 1-4

Samples of the emulsions prepared in Examples 1-4 were sealed into 50 mL clear glass injection vials and stored at room temperature. The appearance of the emulsions was recorded over a 7-day period. The results are provided in the table below. Examples 2,3 and 4 showed good physical stability over the test period. Although there was some separation of the two phases (creaming), the uniform appearance of the emulsions could be restored with gentle shaking.

Example 1, with an oil phase comprising 40% w/w vitamin E, had poor stability and the oil phase readily separated. It was not possible to restore the emulsion to its original uniform state by means of shaking.

Sample	Time of observation				
	Start	3 hours	1 day	3-4 days	7 days
Ex. 1	Stable	Stable	Slight separation, easily redispersed	Separation	Separation
Ex. 2	Stable	Stable	Stable	Stable	Slight separation, easily redispersed
Ex. 3	Stable	Stable	Stable	Slight separation, easily redispersed	Slight separation, easily redispersed
Ex. 4	Stable	Stable	Slight separation, easily redispersed	Slight separation, easily redispersed	Slight separation, easily redispersed

Example 6

Emulsion containing 10 mg/mL midazolam and 25% w/v oil phase

Vitamin E (5 g) and 20 g of soybean oil were weighed into a 50 mL beaker. Midazolam (1 g; R. W. Unwin, Welwyn, UK) was added to the vitamin E/soybean oil and the mixture was warmed and stirred at 30-40°C until the drug had dissolved. Egg yolk phospholipid (1.2 g; lecithin) was weighed into a 250 mL beaker and dispersed into 50 mL of pH 7.4 phosphate buffered saline solution at 30-40°C. Glycerol (2.2 g) was added to the lecithin dispersion. The oil phase was added to the aqueous phase and the two were mixed together by homogenisation for 1 minute at 7000-8000 rpm using a Silverson L4R mixer. The coarse emulsion thus formed was made up to a volume of 100 mL and then passed three times through a Rannie Mini-Lab homogeniser at a pressure of 1000 bar. The final product was a milky white to off-white emulsion.

Example 7

Emulsion containing 10 mg/mL midazolam and 33% w/v oil phase

Vitamin E (6.66 g) and 26.64 g of soybean oil were weighed into a 50 mL beaker. Midazolam (1 g) was added to the vitamin E/soybean oil and the mixture was warmed and stirred at 30-40°C until the drug had dissolved. The emulsion was then prepared according to Example 6.

Example 8

Emulsion containing 10 mg/mL midazolam with polyoxyethylene 20 sorbitan monooleate as additional emulsifier

Vitamin E (5 g) and 20 g of soybean oil are weighed into a 50 mL beaker. Midazolam (1 g) is added to the vitamin E/soybean oil and the mixture is warmed and stirred at 30-40°C until the drug has dissolved. Egg yolk phospholipid (1.2 g; lecithin) and 0.5 g of polyoxyethylene 20 sorbitan monooleate (Sigma) is weighed into a 250 mL beaker and dispersed into 50 mL of pH 7.4 phosphate buffered saline solution at 30-40.C. Glycerol (2.2 g) is added to this aqueous phase. The oil phase is added to the aqueous phase and the two are mixed together by homogenisation for 1 minute at 7000-8000 rpm using a Silverson L4R mixer. The coarse emulsion thus formed is made up to a volume of 100 mL and then passed three times through a Rannie Mini-Lab homogeniser at a pressure of 1000 bar. The final product will be a milky white to off-white emulsion.

Example 9

Emulsion containing 10 mg/mL midazolam with methylcellulose as thickening agent

Vitamin E (6.66 g) and 26.64 g of soybean oil are weighed into a 50 mL beaker. Midazolam (1 g) is added to the vitamin E/soybean oil and the mixture is warmed and stirred at 30-40°C until the drug has dissolved. Egg yolk phospholipid (1.2 g; lecithin) and 0.5 g of methylcellulose (Methocel®

A15LV; Colorcon, Orpington, UK) are weighed into a 250 mL beaker and dispersed into 50 mL of pH 7.4 phosphate buffered saline solution at 30-40°C. Glycerol (2.2 g) is added to the lecithin dispersion. The oil phase is added to the aqueous phase and the two are mixed together by homogenisation for 1 minute at 7000-8000 rpm using a Silverson L4R mixer. The coarse emulsion thus formed is made up to a volume of 100 mL and then passed three times through a Rannie Mini-Lab homogeniser at a pressure of 1000 bar. The final product will be a milky white to off-white emulsion.

Example 10

Emulsion containing 10 mg/mL midazolam with polyoxyl 40 stearate as additional emulsifier and hydroxypropyl methylcellulose as thickening agent

Vitamin E (6.66 g) and 26.64 g of soybean oil are weighed into a 50 mL beaker. Midazolam (1 g) is added to the vitamin E/soybean oil and the mixture is warmed and stirred at 30-40°C until the drug has dissolved. Egg yolk phospholipid (1.2 g; lecithin), 0.5 g of polyoxyl 40 stearate (polyoxyethylene (40) stearate; Sigma) and 0.5 g of hydroxypropyl methylcellulose (Methocel® K4M; Colorcon) are weighed into a 250 mL beaker and dispersed into 50 mL of pH 7.4 phosphate buffered saline solution at 30-40°C. Glycerol (2.2 g) is added to the lecithin dispersion. The oil phase is added to the aqueous phase and the two are mixed together by homogenisation for 1 minute at 7000-8000 rpm using a Silverson L4R mixer. The coarse emulsion thus formed is made up to a volume of 100 mL and then passed three times through a Rannie Mini-Lab homogeniser at a pressure of 1000 bar. The final product will be a milky white to off-white emulsion.

Example 11

Tolerability of midazolam emulsion in sheep

The sheep is an excellent animal model for nasal pharmacokinetic studies with a large nasal cavity and the ability to receive human-sized doses of drugs and formulations. If an irritant drug or formulation is administered intranasally to the sheep, it may cause the animal to sneeze and snort and the extent of sneezing and snorting may be related to the irritancy of the formulation. A group of five sheep were each administered with a midazolam emulsion formulation of identical composition to Example 7 as part of a pharmacokinetic study. Each animal, weighing approximately 55 kg, was administered intranasally with the emulsion at a dose volume of 0.02 mL/kg divided equally between both nostrils i.e. a 55 kg sheep received 0.55 mL of emulsion per nostril. In the 60 minutes following dosing, any incidences of sneezing or snorting were recorded. There were no incidences in any of the five animals during this period, indicating that the formulation was extremely well tolerated.

Claims

1. An oil-in-water emulsion composition for the delivery of a benzodiazepine drug to a patient comprising:
   (a) an oil phase, which phase comprises 10 to 60% (w/v) of the emulsion, and which phase comprises vitamin E in an amount 1 to 35% (w/w of that phase) and a benzodiazepine drug;
   (b) an aqueous phase; and
   (c) an emulsion stabiliser.

2. A composition as claimed in Claim 1, wherein the benzodiazepine drug is alprazolam, bentazepam, bromazepam, brotizolam, camazepam, chlordiazepoxide, cinolazepam, clobazam, clonazepam, clorazepic acid, clorazepate, clotiazepam, clozapine, delorazepam, diazepam, estazolam, ethyl loflazepate, etizolam, fludiazepam, flunitrazepam, flurazepam, halazepam, ketazolam, loprazolam, lorazepam, lormetazepam, metaclazepam, mexazolam, midazolam, nimetazepam, nitrazepam, oxazepam, pinazepam, prazepam, quazepam, temazapem, tetrazepam or triazolam.

3. A composition as claimed in Claim 2, wherein the benzodiazepine drug is alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, estazolam, flurazepam, halazepam, lorazepam, midazolam, nitrazepam, oxazepam, prazepam, quazepam, temazapem or triazolam.

4. A composition as claimed in Claim 3, wherein the benzodiazepine drug is midazolam.

5. A composition as claimed in any one of the preceding claims, wherein the oil phase comprises a non-hydroxylated oil.

6. A composition as claimed in Claim 5, wherein the non-hydroxylated oil is soybean oil, sesame oil, safflower oil, canola oil, corn oil, cottonseed oil, olive oil, cod liver oil or sardine oil.

7. A composition as claimed in Claim 6, wherein the non-hydroxylated oil is soybean oil, sesame oil, canola oil, corn oil or cottonseed oil.

8. A composition as claimed in Claim 7, wherein the non-hydroxylated oil is soybean oil.

9. A composition as claimed in any one of the preceding claims, wherein the oil phase represents 12 to 50% (w/v) of the emulsion.

10. A composition as claimed in Claim 9, wherein the oil phase represents 15 to 40% (w/v) of the emulsion.

11. A composition as claimed in any one of the preceding claims, wherein the oil phase comprises 2.5 to 30% (w/w) vitamin E.

12. A composition as claimed in Claim 11, wherein the oil phase comprises 5 to 25% (w/w) vitamin E.

13. A composition as claimed in any one of the preceding claims, wherein the benzodiazepine drug content of the oil-in-water emulsion is in the range 0.1 to 300 mg/mL.

14. A composition as claimed in any one of the preceding claims, wherein the emulsion stabiliser is one or more thickening and/or emulsifying agents.

15. A composition as claimed in Claim 14, wherein the emulsion stabiliser is an emulsifying agent.

16. A composition as claimed in Claim 15, wherein the emulsifying agent is an ionic surfactant.

17. A composition as claimed in Claim 16, wherein the ionic surfactant is a phospholipid.

18. A composition as claimed in Claim 17, wherein the phospholipid is lecithin.

19. A composition as claimed in any one of Claims 15 to 18, wherein a non-ionic surfactant and/or a thickening agent is/are optionally employed as (a) further emulsion stabiliser(s).

20. A composition as claimed in Claim 19, wherein the non-ionic surfactant is selected from the group consisting of a polyoxyethylene sorbitan fatty acid ester, a polyoxyethylene stearate, a polyoxyethylene castor oil derivative and a polyoxyethylene alkyl ether.

21. A composition as claimed in Claim 19 or Claim 20, wherein the thickening agent is cellulose-based.

22. A composition as claimed in Claim 21, wherein the thickening agent is methylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose or hydroxypropyl methylcellulose.

23. A composition as claimed in any one of the preceding claims, wherein the pH of the aqueous phase is in the range pH 5.0 to 8.0.

24. A composition as claimed in any one of the preceding claims, wherein the emulsion is stable with respect to phase separation for one or more days.

25. The use of a composition as defined in any one of Claims 1 to 24 for the manufacture of a medicament for the administration of a benzodiazepine drug to a patient in need of such administration.

26. Use as claimed in Claim 25 wherein the benzodiazepine drug is midazolam.

27. A method of administering a benzodiazepine drug to a patient, which method comprises administering to the patient a composition as defined in any one of Claims 1 to 24.

28. A method as claimed in Claim 27, wherein the emulsion is administered intranasally.

29. The use of a composition as defined in any one of Claims 1 to 24 in the manufacture of a medicament for the treatment of a condition in which benzodiazepine drug treatment is indicated.

30. The use as claimed in Claim 29, wherein the condition to be treated is an anxiety disorder, a convulsive disorder, disturbed behaviour, a parasomnia, dyspnoea, muscle spasm, emesis, schizophrenia, vertigo or a withdrawal syndrome.

31. The use as claimed in Claim 29, wherein the benzodiazepine drug is given for premedication and/or to induce sedation, hypnosis and/or anterograde amnesia.

32. A process for the preparation of a composition as defined in any one of Claims 1 to 24, which process comprises:

(i) addition of an emulsion stabiliser to an aqueous component to form the aqueous phase;

(ii) addition of vitamin E, and of a benzodiazepine drug, to an oil to form the oil phase; and

(iii) mixing the oil phase and the aqueous phase together.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 02/03005

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/107 A61K31/5513 A61K31/5517 A61K31/355 A61P25/08
A61P25/18 A61P25/20

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)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, EMBASE, PASCAL, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6 193 985 B1 (SONNE METTE RYDAHL) 27 February 2001 (2001-02-27) cited in the application example 9	1-32
A	EP 0 391 369 A (YISSUM RES DEV CO) 10 October 1990 (1990-10-10) tables I,III	1-32
Y	WO 00 24373 A (DAVIS STANLEY STEWART ;ILLUM LISBETH (GB); WEST PHARM SERV DRUG RE) 4 May 2000 (2000-05-04) cited in the application page 6, line 24-26; claims 1-4,17	1-32

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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"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
26 September 2002	07/10/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Zimmer, B

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 02/03005

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97 03651 A (DANBIOSYST UK ;ILLUM LISBETH (GB); WASHINGTON CLIVE (GB); LAWRENCE) 6 February 1997 (1997-02-06) cited in the application page 15, line 23 -page 16, line 17; claim 6	1-32
A	EP 0 163 924 A (ROSHDY ISMAIL) 11 December 1985 (1985-12-11) claim 1	1-32

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 02/03005

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6193985 B1	27-02-2001	AU 697540 B2	08-10-1998
		AU 2670595 A	05-12-1995
		CA 2189328 A1	23-11-1995
		WO 9531217 A1	23-11-1995
		EP 0762896 A1	19-03-1997
		FI 964583 A	15-11-1996
		NO 964832 A	13-01-1997
		NZ 287857 A	24-09-1998
EP 0391369 A	10-10-1990	IL 89856 A	13-05-1993
		IL 93558 A	27-11-1995
		AT 110563 T	15-09-1994
		AU 614465 B2	29-08-1991
		AU 5292790 A	11-10-1990
		CA 2013755 A1	05-10-1990
		DE 69011922 D1	06-10-1994
		DE 69011922 T2	12-01-1995
		EP 0391369 A2	10-10-1990
		JP 2083211 C	23-08-1996
		JP 2290809 A	30-11-1990
		JP 7121857 B	25-12-1995
		US 5364632 A	15-11-1994
		KR 9300044 B1	06-01-1993
WO 0024373 A	04-05-2000	AU 6353699 A	15-05-2000
		EP 1123085 A1	16-08-2001
		WO 0024373 A1	04-05-2000
		NO 20011985 A	23-04-2001
		US 2001055569 A1	27-12-2001
WO 9703651 A	06-02-1997	AU 712621 B2	11-11-1999
		AU 6527596 A	18-02-1997
		CA 2224734 A1	06-02-1997
		EP 0839025 A1	06-05-1998
		WO 9703651 A1	06-02-1997
		GB 2317562 A ,B	01-04-1998
		JP 11509545 T	24-08-1999
		NO 975931 A	17-12-1997
		US 2002025337 A1	28-02-2002
EP 0163924 A	11-12-1985	DE 3416209 A1	21-11-1985
		AT 70441 T	15-01-1992
		DE 3584909 D1	30-01-1992
		EP 0163924 A1	11-12-1985

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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:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

(54) Title: ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

(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.

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ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

[001] This application claims priority under 35 U.S.C. § 119(e) from United States provisional patent application number 61/040,558, which was filed on March 28, 2008, and which is incorporated herein in its entirety.

FIELD OF THE INVENTION

[002] This application relates to the nasal administration of benzodiazepine drugs and combinations thereof.

BACKGROUND OF THE INVENTION

[003] By way of non-limiting example, the benzodiazepine family consists of drugs such as diazepam, lorazepam, and medazepam. The drugs in this family have been observed as possessing sedative, tranquilizing and muscle relaxing properties. They are frequently classified as an 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 (which can be caused by tetanus), the symptoms of drug withdrawal associated with the continuous abuse of central nervous system depressants, and exposure to nerve agents.

[004] 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] 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] 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] 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 may be metabolized. Thus, it may require large doses 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.

[008] 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.

[009] Suppository compositions of benzodiazepine drugs can have a rapid onset of action. However, the inconvenience of suppositories is an obvious impediment to their being administered by anyone outside a very small group of the patient's intimate acquaintances and the patient's professional medical caretakers.

SUMMARY OF THE INVENTION

[010] 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.

[011] 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, medazepam, 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.

[012] 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.

[013] 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.

[014] 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.

[015] 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).

[016] 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 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 of about 30% (w/w).

[017] 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.

[018] 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.

[019] 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); 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.

[020] 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, medazepam, 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.

[021] 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.

[022] 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 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).

[023] 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.

[024] 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).

[025] 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).

[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 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

[031] 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.

DETAILED DESCRIPTION OF THE INVENTION

[032] Provided herein are pharmaceutical compositions of one or more benzodiazepine drugs and methods of using such pharmaceutical compositions. Such pharmaceutical compositions are administered nasally.

[033] 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.

[034] 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.

[035] 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, medazepam, 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.

[036] 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.

[037] 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 alcohol is ethanol (dehydrated, USP). 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 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.

[038] 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.

[039] 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.

[040] 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%, 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). 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 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.

[041] 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 of about 30% (w/w).

[042] 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.

[043] 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.

[044] 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 alcohol 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. 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 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. 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, 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.)

[045] 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. 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, 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. 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 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. 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, 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.)

[046] In some embodiments, the composition 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, substantially all the benzodiazepine drug is in a particulate form. In some embodiments, 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 carrier system in such a composition includes water. In some embodiments, such a liquid carrier system contains water and one or more excipients. In some embodiments, one or more excipients are dissolved or suspended in the carrier system. In some embodiments, at least one such excipient stabilizes the suspension of benzodiazepine particulates in the carrier system. In some embodiments, 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, benzodiazepine particulate suspensions specifically exclude one or more polymeric glycols, such as polyethylene glycol. In some embodiments, benzodiazepine particulate suspensions specifically exclude one or more polymeric glycols having a molecular weight greater than about 200 g/mol. In some embodiments, the composition 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, the composition 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, the composition 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, 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, one or more surfactants and water. In some embodiments, the composition 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, 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 Vitamin E TPGS, methylparaben, propylparaben, propylene glycol, povidone and water. In some embodiments, the composition consists 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, the composition 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, the composition 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.

[047] In some embodiments, the composition 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, substantially all the benzodiazepine drug is in a particulate form. In some embodiments, 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 carrier system in such a composition includes water. In some embodiments, such a liquid carrier system contains water and one or more excipients. In some embodiments, one or more excipients are dissolved or suspended in the carrier system. In some embodiments, at least one such excipient stabilizes the suspension of benzodiazepine particulates in

the carrier system. In some embodiments, 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, benzodiazepine particulate suspensions specifically exclude one or more polymeric glycols, such as polyethylene glycol. In some embodiments, benzodiazepine particulate suspensions specifically exclude one or more polymeric glycols having a molecular weight greater than about 200 g/mol. In some embodiments, the composition comprises 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, the composition 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, the composition 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, 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, the composition 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, 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 Vitamin E TPGS, methylparaben, propylparaben, propylene glycol, an alkyl glycoside, optionally a povidone, and water. In some embodiments, the composition consists 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, the composition 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, the composition 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.

[048] 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); 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.

[049] 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, medazepam, 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.

[050] 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.

[051] 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 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.

[052] 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.

[053] 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.

[054] 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).

[055] 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.

[056] 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).

[057] 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.

[058] 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.

[059] 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.

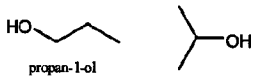
Definitions

[060] 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.

[061] 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.

[062] 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.

[063] 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

[064] 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.)

[065] 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.

[066] 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."

[067] As used herein, unless otherwise qualified, "a" and "an" can mean one or more.

[068] 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.

[069] 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.

[070] 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

[071] 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.

[072] 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.

[073] 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

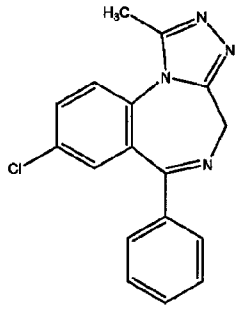
drugs to be administered to one or more mucosal membranes, including to nasal mucosal membranes. This can allow one to administer the drug without hospitalization or unnecessary discomfort. Additionally, in some embodiments of the present invention, such as nasal administration, the digestive system 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.

[074] 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.

[075] In some embodiments, the pharmaceutical composition is used 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.

[076] 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.

[077] **Alprazolam** (8-chloro-6-phenyl-1-methyl-4H-1,2,4-triazolo[4,3-a][1,4]benzodiazepine).



[078] 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.

[079] 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.

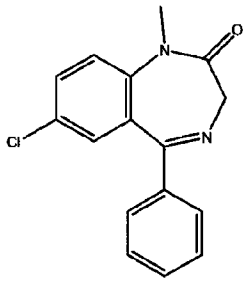
[080] In some embodiments, alprazolam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Alprazolam 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.

[081] 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 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.

[082] 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.

[083] **Diazepam** (7-chloro-1-methyl-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one)



[084] 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.

[085] 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.

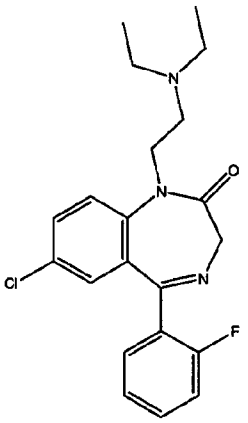
[086] In some embodiments, diazepam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Diazepam 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.

[087] 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 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.

[088] 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.

[089] **Flurazepam** (7-chloro-5-(2-flurophenyl)-2,3-dihydro-1-(2-(diethylamino)ethyl)-1H-1,4-benzodiazepin-2-one)



[090] 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.

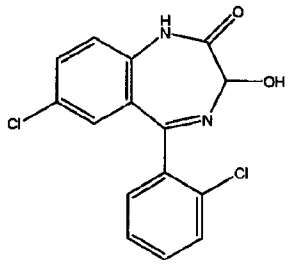
[091] In some embodiments, flurazepam is used alone or in combination with other drugs to provide an anxiolytic effect, an anticonvulsant effect, a sedative effect, a skeletal muscle relaxant effect, an amnesic effect or combinations of the foregoing effects.

[092] 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.

[093] 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 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.

[094] 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.

[095] **Lorazepam** (7-chloro-5-(2-chlorophenyl)-3-hydroxy-1,3-dihydro-2H-1,4-benzodiazepin-2-one)



[096] 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.

[097] 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.

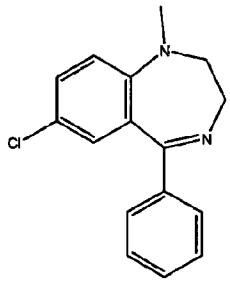
[098] In some embodiments, lorazepam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Lorazepam 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.

[099] 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 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.

[0100] 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.

[0101] **Medazepam** ((7-chloro-1-methyl-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepine)



[0102] 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.

[0103] 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.

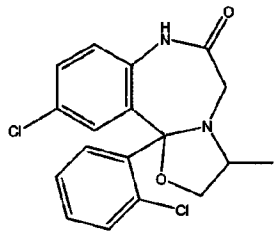
[0104] In some embodiments, medazepam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Medazepam 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.

[0105] 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 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.

[0106] 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.

[0107] **Mexazolam** (10-Chloro-11b-(2-chlorophenyl)-1,3,7,11b-tetrahydro-3-methyloxazolo[3,2-d][1,4]benzodiazepin-6(5H)-one)



[0108] 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.

[0109] 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.

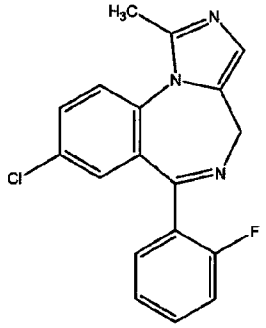
[0110] In some embodiments, mexazolam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Mexazolam 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.

[0111] 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 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.

[0112] 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.

[0113] **Midazolam** (8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo(1,5-a)benzodiazepine).



[0114] 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.

[0115] 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.

[0116] 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.

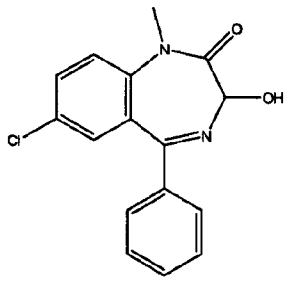
[0117] In some embodiments, midazolam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Midazolam 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.

[0118] 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 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.

[0119] 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.

[0120] **Temazepam** (7-chloro-1-methyl-5-phenyl-3-hydroxy-1,3-dihydro-2H-1,4-benzodiazepin-2-one)



[0121] 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.

[0122] 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.

[0123] 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

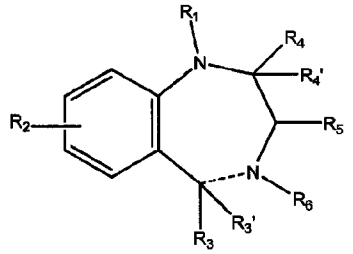
seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Temazepam may be administered by the patient or other person (such as a healthcare professional) while the patient is in a non-seizing state to protect against seizure. Even where protection 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.

[0124] 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 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.

[0125] 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

[0126] 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.

[0127] 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

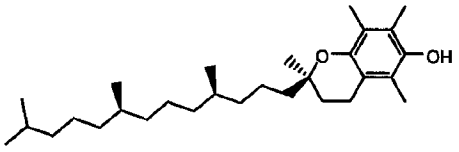
acid, succinic acid, sulfuric acid, tartaric acid (+ L), thiocyanic acid, toluenesulfonic acid (p) and undecylenic acid. Other pharmaceutically acceptable acids may be pharmaceutically acceptable acidic (anionic) polymers or pharmaceutically acceptable amphoteric polymers. One skilled in the art will 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.

[0128] 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.

[0129] 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

[0130] 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

[0131] 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.

[0132] 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.

[0133] 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.

[0134] 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.

[0135] 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

[0136] 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).

[0137] 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.

[0138] 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.

[0139] 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.

[0140] 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.

[0141] 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

[0142] 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.

[0143] 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

[0144] 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.

[0145] 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

[0146] 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.

[0147] 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

[0148] 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.

[0149] 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

[0150] 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.

[0151] 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

[0152] 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.

[0153] 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

[0154] 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.

[0155] 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

[0156] 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.

[0157] 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

[0158] 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.

[0159] 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

[0160] 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.

[0161] 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.

[0162] 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.

[0163] 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.

Formulation Process

[0164] 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.

[0165] The aforementioned formulations are preferably sterile with a bacteria count of 10 below the allowable level on a per mL basis. Additionally, pathogens are preferably absent.

[0166] 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.

[0167] 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

[0168] 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.

[0169] 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.

[0170] 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.

[0171] 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.

[0172] 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.

[0173] 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.

[0174] 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.

[0175] 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

[0176] 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

[0177] 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.

[0178] 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

[0179] 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.

[0180] 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

[0181] 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.

[0182] 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

[0183] 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.

[0184] 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

[0185] 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.

[0186] 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

[0187] 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.

[0188] 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

[0189] 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.

[0190] 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

[0191] 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.

[0192] 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.

[0193] 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

[0194] The invention will now be illustrated with reference to the following illustrative, non-limiting examples.

Example 1

[0195] 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

5.0 mg/0.1mL	Diazepam
70.0 mg	α-tocopherol
0.1 mL	ethanol (qs ad to 0.1 mL)

Example 2

[0196] 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

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

[0197] 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.

[0198] 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

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

[0199] 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

[0200] 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.

[0201] 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

[0202] 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

[0203] Solutions 00 and 02 (Example 3) and Suspensions 01 and 03 (Example 4) were set up on stability at 25°C / 60% RH, 30°C / 65% RH and 40°C / 75% RH. One batch each of four 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

[0204] 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>.

[0205] 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, 5-11, 5-12, 5-13, 5-14, and 5-15.

[0206] 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.

[0207] 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%

[0208] 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

Solution02, 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%	100.5	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 Diazepam (%)	90.0 to 110.0%	102.8	102.6	100.9	104.3	101.3	101.8	103.6	100.7	104.3	99.4
Impurities (%) (1)											
Nordazepam Related Compound B	NMT 0.3%	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Related Compound A	NMT 0.1%	ND	ND	ND	0.004	ND	0.004	0.053	0.005	0.013	0.289
Unknown	NMT 0.01%	ND	0.01	0.02	0.034	0.026	0.036	0.08	0.038	0.046	0.157
Total	NMT 0.1%	0.008	0.008	0.008	0.008	0.008	0.007	0.007	0.008	0.007	0.018
Methylparaben (%)	NMT 1.0%	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.5
	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
St. Dev.	0.0097	0.0095	0.8884	9.0649
% RSD	7.14	6.76	8.34	8.34

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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

Table 5-12: Suspension 01 25°C/60% RH spray content uniformity results

Sample	Weight Collected, g	Weight Actuated, g	Diazepam Recovered, mg	% Diazepam Recovered

1	0.12873	0.12999	12.85366	91.81
2	0.14011	0.14247	13.68122	97.72
3	0.14515	0.14757	14.09449	100.67
4	0.13205	0.13347	14.18775	101.34
5	0.14554	0.14743	14.48202	103.44
6	0.14473	0.14682	14.39897	102.85
7	0.13229	0.13411	14.87853	106.28
8	0.14357	0.14581	14.82712	105.91
9	0.14741	0.14940	14.86732	106.20
Average	0.13995	0.14190	14.252	101.80
St. Dev.	0.0070	0.0074	0.6602	4.7154
% RSD	5.03	5.18	4.63	4.63

Table 5-13: Suspension 01 40°C/75% RH spray content uniformity results

Sample	Weight Collected, g	Weight Actuated, g	Diazepam Recovered, mg	% Diazepam Recovered
1	0.14411	0.14869	13.04770	93.20
2	0.14066	0.14151	13.23277	94.52
3	0.13012	0.13485	13.78126	98.44
4	0.14667	0.14879	13.36970	95.50
5	0.14294	0.14338	12.54309	89.59
6	0.13797	0.14253	13.25396	94.67
7	0.13374	0.13594	13.41984	95.86
8	0.12388	0.12559	14.34944	102.50
9	0.13790	0.14011	13.88564	99.18
Average	0.13755	0.14015	13.431	95.94
St. Dev.	0.0073	0.0073	0.5223	3.7310
% RSD	5.28	5.19	3.89	3.89

Table 5-14: Suspension 03 25°C/60% RH spray content uniformity results

Sample	Weight Collected, g	Weight Actuated, g	Diazepam Recovered, mg	% Disazepam Recovered
1	0.13604	0.13897	25.93418	92.62
2	0.14608	0.14792	26.21721	93.63

3	0.15294	0.15425	30.05570	107.34
4	0.14728	0.14910	25.78804	92.10
5	0.15352	0.15493	26.60721	95.03
6	0.15242	0.15401	29.51030	105.39
7	0.15118	0.15254	28.43104	101.54
8	0.15322	0.15556	28.03664	100.13
9	0.15197	0.15393	26.82906	95.82
Average	0.14941	0.15125	27.490	98.18
St. Dev.	0.0057	0.0053	1.5812	5.6472
% RSD	3.79	3.50	5.75	5.75

Table 5-15: Suspension 03 40°C/75% RH spray content uniformity results

Sample	Weight Collected, g	Weight Actuated, g	Diazepam Recovered, mg	% Disazepam Recovered
1	0.13574	0.13797	28.14588	100.52
2	0.13639	0.13803	27.04437	96.59
3	0.14082	0.14195	26.78985	95.68
4	0.12962	0.13249	29.07192	103.83
5	0.12518	0.12683	27.39785	97.85
6	0.14423	0.14541	28.50133	101.79
7	0.13922	0.14096	27.34617	97.66
8	0.14146	0.14313	27.17415	97.05
9	0.14902	0.15344	27.20939	97.18
Average	0.13796	0.14002	27.631	98.68
St. Dev.	0.0073	0.0076	0.7642	2.7294
% RSD	5.28	5.43	2.77	2.77

Example 6

[0209] All of the solutions and suspensions described in Examples 3 and 4 are formulated as described in Examples 3 and 4, 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 and suspensions with added alkyl glycoside may then be put up on stability as described in Example 5, *mutatis mutandis*.

Example 7

[0210] The solutions and suspensions of Examples 3, 4 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 or suspension as described in Examples 3, 4 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 and suspensions administered by the intranasal administration route.

[0211] 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

[0212] The solutions and suspensions of Examples 3, 4 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 or suspension as described in Examples 3, 4 and 6, with the solution or suspension 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 suspension 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

[0213] The above-described solutions and/or suspensions 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 or suspension 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

[0214] The above-described solutions and/or suspensions can be evaluated for efficacy in a suitable animal model. Briefly, for each dose of suspension or 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 or suspension as described herein is administered intranasally to the animal. The efficacy of the dose of the solution and/or suspension 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.

[0215] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

CLAIMS

WHAT IS CLAIMED IS:

1. A pharmaceutical composition for nasal administration comprising:

(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); and

(c) 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.

2. The pharmaceutical composition 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. The pharmaceutical composition of claim 2, 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, medazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, any pharmaceutically-acceptable salts thereof, and any combinations thereof.

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

5. The pharmaceutical composition of claim 1, wherein the benzodiazepine drug comprises benzodiazepine microparticles, nanoparticles, or combinations thereof.

6. The pharmaceutical composition of claim 5, wherein the benzodiazepine nanoparticles have an effective average particle size of less than about 5000 nm.

7. The pharmaceutical composition 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 composition 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 composition of claim 1, wherein 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.

10. The pharmaceutical composition of claim 1, wherein the benzodiazepine drug is present in the pharmaceutical composition in a concentration from about 1 mg/mL to about 600 mg/mL.

11. The pharmaceutical composition of claim 1, wherein the benzodiazepine drug is present in the pharmaceutical composition in a concentration from about 10 mg/mL to about 250 mg/mL.

12. The pharmaceutical composition of claim 11, wherein the benzodiazepine is present in the pharmaceutical composition in a concentration from about 20 mg/mL to about 50 mg/mL.

13. The pharmaceutical composition 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 composition of claim 13, wherein the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from about 60% to about 75% (w/w).

15. The pharmaceutical composition 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 composition 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. The composition of one of claims 1 - 16, further comprising 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.

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

19. The composition of claim 18, wherein the pharmaceutically-acceptable formulation about 0.01% to 1% (w/w) of an alkyl glycoside.

20. A method of treating a patient with a disorder which may be treatable with a benzodiazepine drug, comprising:

(a) 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 10% to about 70% (w/w).

21. The method of claim 20, 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).

22. The method of claim 21, wherein said patient is a human.

23. The method of claim 20, 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, medazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, or any pharmaceutically-acceptable salts thereof, and any combinations thereof.

24. The method of claim 23, wherein the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof.

25. The method of claim 20, wherein the benzodiazepine drug comprises benzodiazepine microparticles, nanoparticles, or combinations thereof.

26. The method of claim 25, wherein the benzodiazepine nanoparticles have an effective average particle size of less than about 5000 nm.

27. The method of claim 20, 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.

28. The method of claim 20, 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.

29. The method of claim 20, wherein 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.

30. The method of claim 20, wherein the benzodiazepine drug is present in the pharmaceutical composition in a concentration from about 1 mg/mL to about 600 mg/mL.

31. The method of claim 30, wherein the benzodiazepine drug is present in the pharmaceutical composition in a concentration of from about 10 mg/mL to about 250 mg/mL.

32. The method of claim 31, wherein the benzodiazepine drug is present in the pharmaceutical composition in a concentration of from about 20 mg/mL to about 50 mg/mL.

33. The method of claim 20, wherein the pharmaceutical composition 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).

34. The method claim 33, wherein the pharmaceutical composition 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).

35. The method of claim 20, wherein the pharmaceutical composition comprises one or more alcohols or glycols, or any combinations thereof, in an amount from about 15% to about 55% (w/w).

36. The method of claim 35, wherein the pharmaceutical composition comprises one or more alcohols or glycols, or any combinations thereof, in an amount from about 25% to about 40% (w/w).

37. The method of claim 20, wherein 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.

38. The method of claim 20, wherein the composition is in a pharmaceutically-acceptable spray formulation.

39. The method of claim 38, wherein the benzodiazepine is administered in a therapeutically effective amount from about 1 mg to about 20 mg.

40. The method of claim 39, wherein said pharmaceutical composition is in a pharmaceutically-acceptable spray formulation having volume from about 10 μL to about 200 μL.

41. The method of claim 40, wherein 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.

42. The method of claim 40, wherein the administration of the pharmaceutical composition comprises spraying at least a portion of the therapeutically effective amount of the benzodiazepine into each nostril.

43. The method of claim 42, wherein the 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.

44. The method of claim 43, further comprising, optionally after a pre-selected time delay, administering at least a fourth quantity of the pharmaceutical composition to the second nostril.

45. The method of claim 43, wherein 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.

46. The composition of claim 20, wherein the pharmaceutically-acceptable formulation comprises at least about 0.01% (w/w) of an alkyl glycoside.

47. The composition of claim 21, wherein the pharmaceutically-acceptable formulation about 0.01% to 1% (w/w) of an alkyl glycoside.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor:	CARTT; Steve et al.	Group Art Unit:	1612
Serial Number:	14/527,613	Examiner:	Milligan, Adam
Filing or 371 (c) Date:	2014-10-29	**CONFIRMATION NO:**	**2149**
Title:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS		

FILED ELECTRONICALLY ON: January 11, 2017

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

A. ☐ *37 CFR § 1.97 (b).* This Information Disclosure Statement should be considered by the Office because:

☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);

-- OR --

☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;

-- OR --

☐ (3) It is being filed before the mailing of a first Office action on the merits;

-- OR --

☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.

B. ☒ *37 CFR § 1.97(c).* Although this Information Disclosure Statement is being filed after the period specified in *37 CFR § 1.97(b),* above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97 (e) provided concurrently herewith;

-- OR --

☒ a fee of $90.00 as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☐ *37 CFR § 1.97 (d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in § 1.97 (e);

-- AND --

ii. a fee of $180.00 as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☐ *37 CFR §1.97 (e).* Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);

-- AND/OR --

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);

-- AND/OR --

☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay.

F. ☒ *37 CFR §1.98 (a) (2).* The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☒ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 is NOT enclosed.

-- AND/OR --

☒ Copies of Foreign Patent Documents and/or Non Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).

G. ☒ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☒ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☐ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: _____

Information Disclosure Statement(s) filed on: _____

AND

☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

I. ☒ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $90.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No.35401-716.301).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: January 11, 2017

By: /Matthew V. Grumbling/
Matthew V. Grumbling, Reg. No. 44,427

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/527,613	10/29/2014	Steve Cartt	35401-716.301	2149

21971 7590 04/21/2017

WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

EXAMINER
MILLIGAN, ADAM C

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
04/21/2017	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@wsgr.com

Office Action Summary	Application No. 14/527,613	Applicant(s) CARTT ET AL.	
	Examiner ADAM C. MILLIGAN	Art Unit 1612	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *1/10/2017*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *23,25-30,33-51,53-56 and 60-65* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *23,25-30,33-51,53-56 and 60-65* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

Applicants' arguments, filed 1/10/2017, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Nonstatutory Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 23, 25-30, 33-51, 53-56 and 60-65 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 8,895,546. Although the claims at issue are not identical, they are not patentably distinct from each other because it is obvious to administer a composition "for nasal administration" to the nasal mucosal membranes. see MPEP 804.01(E)

Claims 23, 25-30, 33-51, 53-56 and 60-65 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 20, 22-24, 27-36, 40-45 and 48-54 of copending Application No. 12/413,439 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because it would have been obvious to one of ordinary skill in the art to choose from the recited components of the copending applications to arrive at the instantly claimed subject matter.

Applicants' attention is also directed to recently filed claims 66-84 of copending Application No. 15/470,498. Similar to the 12/413,439 application, the claims in the 15/470,498 application do not appear to be patentably distinct from the present claims because it would have been obvious to one of ordinary skill in the art to choose from the recited components of the copending applications to arrive at the instantly claimed subject matter.

Conclusion

No claims allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ADAM MILLIGAN whose telephone number is (571)270-7674. The examiner can normally be reached on M-F 9:00-5:00 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fred Krass can be reached on (571)272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ADAM C MILLIGAN/
Primary Examiner, Art Unit 1612

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	14527613
Filing Date	10-29-2014
First Named Inventor	CARTT; Steve
Art Unit	1612
Examiner Name	Milligan, Adam
Attorney Docket Number	35401-716.301

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	001	US-20040101482	05-27-2004	SANDERS; Mark	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	001	CN-1303674-A	07-18-2001	INST OF MEDICAL INDUSTRY SHAND [CN]	English abstract provided	☒
	002	EP-1208863-A2	05-29-2002	UNISIA JECS CORP [JP]		☐
	003	JP-2011516425-A	05-26-2011	HALE BIOPHARMA VENTURES LLC [US], et al.	See WO-2009121039-A2 for English	☒
	004	WO-03004015-A1	01-16-2003	WEST PHARM SERV DRUG RES LTD [GB], et al.		☐
	005	WO-2009121039-A2	10-01-2009	HALE BIOPHARMA VENTURES LLC [US], et al.		☐

Examiner Signature	/ADAM C MILLIGAN/	Date Considered	04/17/2017

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /A.C.M/

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 2

Complete if Known	
Application Number	14527613
Filing Date	10-29-2014
First Named Inventor	CARTT; Steve
Art Unit	1612
Examiner Name	Milligan, Adam
Attorney Docket Number	35401-716.301

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author(in CAPITAL LETTERS),title of the article(when appropriate), title of the item (book,magazine,journal,serial,symposium,catalog,etc.),date,page(s),volume-issue number(s),publisher, city and/or country where published.	T[2]
	001	Canadian Patent Application No. 2756690 Examiner's Report dated October 20, 2015	☐
	002	Chinese Patent Application No. 201280039077.9 Office Action dated November 21, 2016.	☒
	003	Chinese Patent Application No. 2012800390779 Second Office Action dated August 11, 2015	☒
	004	Chinese Patent Application No. 201280039077.9 Third Office Action dated March 17, 2016.	☒
	005	European Patent Application No. 12801372.9 Extended EP Search Report dated March 26, 2015.	☐
	006	European Patent Application No. 12801372.9 Communication dated July 5, 2016.	☐
	007	Japanese Patent Application No. 2014-515967 Office Action dated March 30, 2016.	☒
	008	Japanese Patent Application No. 2014-515967 Office Action dated November 28, 2016.	☒
	009	Newman. Aerosol deposition consideration in inhalation therapy. Chest 152S-160S (1985).	☐
	010	U.S. Patent Application No. 12/413,439 Office Action dated July 14, 2016.	☐
	011	U.S. Patent Application No. 12/413,439 Office Action dated October 5, 2015	☐
	012	U.S. Patent Application No. 14/948,081 Office Action dated October 31, 2016.	☐
	013	U.S. Patent Application No. 12/116,842 Office Action mailed July 8, 2015.	☐
	014	U.S. Patent Application No. 14/021,988 Office Action mailed May 22, 2015.	☐

Examiner Signature	/ADAM C MILLIGAN/	Date Considered	04/17/2017

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 1 Applicant's unique citation designation number (optional). 2 Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /A.C.M/

Document Description: Application Data Sheet to update/correct info
Doc Code: ADS.CORR

CORRECTED ADS FORM

Application Number	14527613
Title of Invention	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

Inventor Information

****If no data is shown, no data has been corrected****

	Data of Record	Updated Data
Order Number		
Name		
Residence Information		
Residency		
City		
State		
Country of Residence		
Mailing Address of Inventor		
Address 1		
Address 2		
City,State/Province, Postal Code		
Country		

Document Description: Application Data Sheet to update/correct info
Doc Code: ADS.CORR

Application Information

	Data of Record	Updated Data
Title of Invention	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS	
Attorney Docket Number	35401-716.301	
Entity Type	Small	

Domestic Benefit/National Stage Information

****If no data is shown, no data has been corrected****

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121,365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S. C. 119(e) or 120, and 37 CFR 1.78(a).

		Data of Record	Updated Data
	Prior Application Status		
	Application Number		
	Continuity Type		
	Prior Application Number		
	Filing Date (YYYY-MM-DD)		
	Patent Number		
	Issue Date (YYYY-MM-DD)		

Foreign Priority Information

Document Description: Application Data Sheet to update/correct info
Doc Code: ADS.CORR

****If no data is shown, no data has been corrected****

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX) the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

		Data of Record	Updated Data
	Application Number		
	Country		
	Filing Date		
	Access Code		

Applicant Information

****If no data is shown, no data has been corrected****
Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

	Data of Record	Updated Data
Applicant Type	ASG	
If applicant is the legal representative, indicate the authority to file the patent application, the inventor is		
Name of the Deceased or Legally Incapacitated Inventor		
Applicant is an Organization	Yes	
Name		
Organization Name	~~Hale Biopharma Ventures~~	Hale Biopharma Ventures, LLC
Address 1	1042-B North El Camino Real, Suite 430	
Address 2		

City,State/Province,Postal Code	Encinitas CA 92024	
Country	US	
Phone Number		
Fax Number		
Email Address		

Assignee Information including Non-Applicant Assignee Information

****If no data is shown, no data has been corrected****
Providing this information in the application data sheet does not substitute for compliance with any requirement of part 3 of Title 37 of the CFR to have an assignment recorded in the Office

	Data of Record	Updated Data
Order		
Applicant is an Organization		
Name		
Organization Name		
Mailing Address		
Address 1		
Address 2		
City,State/Province,Postal Code		
Country		
Phone Number		
Fax Number		
Email Address		

Signature

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b).

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Matthew V. Grumbling/	Registration Number	44,427
First Name	Matthew	Last Name	Grumbling

Electronic Patent Application Fee Transmittal

Application Number:	14527613
Filing Date:	29-Oct-2014
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	
Filer:	Matthew Virgil Grumbling
Attorney Docket Number:	35401-716.301

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
PROCESSING FEE, EXCEPT PROV. APPLS.	2830	1	70	70
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**70**

Electronic Acknowledgement Receipt

EFS ID:	29039789
Application Number:	14527613
International Application Number:	
Confirmation Number:	2149
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	
Customer Number:	21971
Filer:	Matthew Virgil Grumbling
Filer Authorized By:	
Attorney Docket Number:	35401-716.301
Receipt Date:	26-APR-2017
Filing Date:	29-OCT-2014
Time Stamp:	17:52:38
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$70
RAM confirmation Number	042717INTEFSW00007185232415
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Application Data Sheet to update/ correct info	CorrectedADS.pdf	65160 37f8d1fe753c066ea78aee88d6118839389b7790	no	5
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30606 1e8fbfbfcc491633d9f36717591cb420131dd9b3	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	95766		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Doc Code: PA..

Document Description: Power of Attorney

PTO/AIA/82A (07-12)

Approved for use through 11/30/2014. OMB 0651-0035

U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B or equivalent) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5. If the Power of Attorney by Applicant form is not accompanied by this transmittal form or an equivalent, the Power of Attorney will not be recognized in the application.

Application Number	14/527,613
Filing Date	10/29/2014
First Named Inventor	Steve Cartt
Title	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
Art Unit	1629
Examiner Name	Adam C. Milligan
Attorney Docket Number	35401-716.301

SIGNATURE of Applicant or Patent Practitioner

Signature	/Matthew V. Grumbling/	Date	April 26, 2017
Name	Matthew V. Grumbling	Telephone	858-350-2332
Registration Number	44,427		

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications.

■ *Total of 1 forms are submitted.

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Doc Code: PA..

Document Description: Power of Attorney

PTO/AIA/82B(07-12)

Approved for use through 11/30/2014. OMB 0651-0035

U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in the attached transmittal letter.

☒ I hereby appoint Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A or equivalent):

21971

OR

☐ I hereby appoint Practitioner(s) named below as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A or equivalent):

Name	Registration Number		Name	Registration Number

Please recognize or change the correspondence address for the application identified in the attached transmittal letter to:

☐ The address associated with the above-mentioned Customer Number.

OR

☐ The address associated with Customer Number:

OR

☐ Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the Applicant:

☐ Inventor or Joint Inventor

☐ Legal Representative of a Deceased or Legally Incapacitated Inventor

☒ Assignee or Person to Whom the Inventor is Under an Obligation to Assign

☐ Person Who Otherwise Shows Sufficient Proprietary Interest (*e.g.*, a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document)

SIGNATURE of Applicant for Patent

Signature		Date	4/12/13
Name	David F. Hale	Telephone	858-756-2480
Title and Company	Chairman and CEO, Hale Biopharma Ventures, LLC		

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms for more than one signature, see below *.

☒ *Total of 2 forms are submitted.

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Acknowledgement Receipt

EFS ID:	29040107
Application Number:	14527613
International Application Number:	
Confirmation Number:	2149
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Customer Number:	21971
Filer:	Matthew Virgil Grumbling/Lori Ford
Filer Authorized By:	Matthew Virgil Grumbling
Attorney Docket Number:	35401-716.301
Receipt Date:	26-APR-2017
Filing Date:	29-OCT-2014
Time Stamp:	18:01:20
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	35401_716_301_POA_Fully_Executed.PDF	2012475 71286a4e9af974272c3eba6a288d936ba99cfc5f	no	3

Warnings:

Information:	
Total Files Size (in bytes):	2012475

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: Inventors: Steve Cartt, et al. Serial No.: 14/527,613 Filing Date: October 29, 2014 Title: ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS	Group Art Unit: 1612 Confirmation No.: 2149 Examiner: Adam C. Milligan Customer No.: 21971

ELECTRONICALLY FILED ON APRIL 26, 2017

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CORRECTION OF APPLICANT NAME (37 C.F.R. 1.46(c)(1))

Commissioner:

The Applicant's name was in error on the Application Data Sheet filed on October 29, 2014. A Corrected Application Data Sheet has been filed which corrects the Applicant's name as follows:

Incorrect: Hale Biopharma Ventures

Correct: Hale Biopharma Ventures, LLC

A Statement under 37 CFR 3.73(c) is filed herewith.

Issuance of a corrected Filing Receipt is respectfully requested.

Applicant believes no fee is due, however if Applicant is not correct, the USPTO is authorized to charge Deposit Account No. 23-2415, referencing Docket No. 35401-716.301.

CONCLUSION

The Commissioner is hereby authorized to charge any additional fees that may be required, or credit any overpayment, including petition fees and extension of time fees, to Deposit Account No. 23-2415 (Attorney Docket No. 35401-716.301).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI
Professional Corporation

Date: April 26, 2017

By: /Matthew V. Grumbling/
Matthew V. Grumbling.
Reg. No. 44,427

650 Page Mill Road
Palo Alto, CA 94304
Direct Dial: (858) 350-2332
Customer No. 021971

PTO/AIA/96 (08-12)
Approved for use through 01/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: Hale Biopharma Ventures, LLC

Application No./Patent No.: 14/527,613 Filed/Issue Date: October 29, 2014

Titled: ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

Hale Biopharma Ventures, LLC, a limited liability company

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. ☑ The assignee of the entire right, title, and interest.

2. ☐ An assignee of less than the entire right, title, and interest (check applicable box):

   ☐ The extent (by percentage) of its ownership interest is _____%. Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

   ☐ There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. ☐ The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. ☐ The recipient, via a court proceeding or the like (*e.g.*, bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

A. ☑ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 036803, Frame 0604, or for which a copy thereof is attached.

B. ☐ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: _____ To: _____

   The document was recorded in the United States Patent and Trademark Office at

   Reel _____, Frame _____, or for which a copy thereof is attached.

2. From: _____ To: _____

   The document was recorded in the United States Patent and Trademark Office at

   Reel _____, Frame _____, or for which a copy thereof is attached.

PTO/AIA/96 (08-12)
Approved for use through 01/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(c)

3. From: _____ To: _____

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4. From: _____ To: _____

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☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☑ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Matthew V. Grumbling/	April 26, 2017
Signature	Date
Matthew V. Grumbling	44427
Printed or Typed Name	Title or Registration Number

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Acknowledgement Receipt

EFS ID:	29041400
Application Number:	14527613
International Application Number:	
Confirmation Number:	2149
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Customer Number:	21971
Filer:	Matthew Virgil Grumbling/Lori Ford
Filer Authorized By:	Matthew Virgil Grumbling
Attorney Docket Number:	35401-716.301
Receipt Date:	26-APR-2017
Filing Date:	29-OCT-2014
Time Stamp:	20:28:10
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Corrected Filing Receipt	35401_716_301_Request_Correction_Applicant_Name.pdf	22694 b1b64c4dc136dac902dd77d8a5a64edc625445b6	no	2

Warnings:

Information:					
2	Assignee showing of ownership per 37 CFR 3.73	35401_716_301_3_73c.pdf	126365 b94116e24956f0ab5db1ef35765040ea706f310c	no	3
Warnings:					
Information:					
		Total Files Size (in bytes):	149059		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/527,613	10/29/2014	Steve Cartt	35401-716.301

CONFIRMATION NO. 2149

21971
WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

POA ACCEPTANCE LETTER

OC000000090984515

Date Mailed: 04/28/2017

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 04/26/2017.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/zabraha/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
14/527,613	10/29/2014	1612	1480	35401-716.301	37	1

CONFIRMATION NO. 2149

CORRECTED FILING RECEIPT

21971
WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

OC000000090984552

Date Mailed: 04/28/2017

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Steve Cartt, Union City, CA;
David Medeiros, South San Francisco, CA;
Garry Thomas Gwozdz, Jim Thorpe, PA;
Andrew Loxley, Residence Not Provided;
Mark Mitchnick, East Hampton, NY;
David Hale, San Diego, CA;
Edward T. Maggio, San Diego, CA;

Applicant(s)

Hale Biopharma Ventures, LLC, Encinitas, CA;

Power of Attorney: The patent practitioners associated with Customer Number 21971

Domestic Priority data as claimed by applicant

This application is a CON of 13/495,942 06/13/2012 PAT 8895546
which is a CIP of 12/413,439 03/27/2009
which claims benefit of 61/040,558 03/28/2008
and said 13/495,942 06/13/2012
claims benefit of 61/497,017 06/14/2011
and claims benefit of 61/570,110 12/13/2011

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: No

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 11/20/2014

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 14/527,613**

Projected Publication Date: Not Applicable

Non-Publication Request: No

Early Publication Request: No

**** SMALL ENTITY ****

Title

ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

Preliminary Class

424

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor

community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

Doc Code: DIST.E.FILE Document Description: Electronic Terminal Disclaimer - Filed	PTO/SB/25 PTO/SB/26 U.S. Patent and Trademark Office Department of Commerce

Electronic Petition Request	**TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING "REFERENCE" APPLICATION AND TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT**
Application Number	14527613
Filing Date	29-Oct-2014
First Named Inventor	Steve Cartt
Attorney Docket Number	35401-716.301
Title of Invention	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

☒ Filing of terminal disclaimer does not obviate requirement for response under 37 CFR 1.111 to outstanding Office Action

☒ This electronic Terminal Disclaimer is not being used for a Joint Research Agreement.

Owner	Percent Interest
Hale Biopharma Ventures, LLC	100 %

The owner(s) of percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending reference Application Number(s)

15470498 filed on 03/27/2017

12413439 filed on 03/27/2009

as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the reference application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term of any patent granted on said reference application, "as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application," in the event that any such patent granted on the pending reference application: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

The owner(s) with percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of prior patent number(s)

8895546

as the term of said prior patent is presently shortened by any terminal disclaimer. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the prior patent, "as the term of said prior patent is presently shortened by any terminal disclaimer," in the event that said prior patent later:
- expires for failure to pay a maintenance fee;
- is held unenforceable;
- is found invalid by a court of competent jurisdiction;
- is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
- has all claims canceled by a reexamination certificate;
- is reissued; or
- is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

(●) Terminal disclaimer fee under 37 CFR 1.20(d) is included with Electronic Terminal Disclaimer request.

( ) I certify, in accordance with 37 CFR 1.4(d)(4), that the terminal disclaimer fee under 37 CFR 1.20(d) required for this terminal disclaimer has already been paid in the above-identified application.

Applicants claims the following fee status:

(●) Small Entity

( ) Micro Entity

( ) Regular Undiscounted

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

THIS PORTION MUST BE COMPLETED BY THE SIGNATORY OR SIGNATORIES

I certify, in accordance with 37 CFR 1.4(d)(4) that I am:

(●) An attorney or agent registered to practice before the Patent and Trademark Office who is of record in this application

Registration Number 44427

( ) A sole inventor

( ) A joint inventor; I certify that I am authorized to sign this submission on behalf of all of the inventors as evidenced by the power of attorney in the application

( ) A joint inventor; all of whom are signing this request

Signature	/Matthew V. Grumbling/

Name	Matthew V. Grumbling

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).
Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

Electronic Patent Application Fee Transmittal

Application Number:	14527613
Filing Date:	29-Oct-2014
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Filer:	Matthew Virgil Grumbling
Attorney Docket Number:	35401-716.301

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
STATUTORY OR TERMINAL DISCLAIMER	2814	1	160	160
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**160**

Doc Code: DISQ.E.FILE
Document Description: Electronic Terminal Disclaimer – Approved

Application No.: 14527613

Filing Date: 29-Oct-2014

Applicant/Patent under Reexamination: Cartt

Electronic Terminal Disclaimer filed on April 28, 2017

☒ APPROVED

This patent is subject to a terminal disclaimer

☐ DISAPPROVED

Approved/Disapproved by: Electronic Terminal Disclaimer automatically approved by EFS-Web

U.S. Patent and Trademark Office

Electronic Acknowledgement Receipt

EFS ID:	29067974
Application Number:	14527613
International Application Number:	
Confirmation Number:	2149
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Customer Number:	21971
Filer:	Matthew Virgil Grumbling
Filer Authorized By:	
Attorney Docket Number:	35401-716.301
Receipt Date:	28-APR-2017
Filing Date:	29-OCT-2014
Time Stamp:	17:35:57
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$160
RAM confirmation Number	050117INTEFSW00005199232415
Deposit Account	232415
Authorized User	Matthew Grumbling

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Electronic Terminal Disclaimer-Filed	eTerminal-Disclaimer.pdf	37089 3e8115dbbd8b85fcd7ecf647c83150183b2e3b75	no	3
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30737 522c2cb58b10ec31bc733daeac3dc2a502eea2a9	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	67826		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

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If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: Inventors: Steve Cartt, et al. Serial No.: 14/527,613 Filing Date: October 29, 2014 Title: ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS	Group Art Unit: 1612 Confirmation No.: 2149 Examiner: Adam C. Milligan Customer No.: 21971

ELECTRONICALLY FILED ON APRIL 28, 2017

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO FINAL OFFICE ACTION

Commissioner:

This paper is submitted in response to the Final Office Action dated April 21, 2017. The Commissioner is authorized to charge any additional fees which may be required to Deposit Account No. 23-2415 (Docket No. 35401-716.301).

Remarks begin on page **2**.

REMARKS

In response to the Final Office Action dated April 21, 2017, Applicant requests reconsideration in view of Terminal Disclaimers E-filed and approved April 28, 2017. Claims 23, 25-30, 33-51, 53-56, and 60-65 are currently pending. Applicants respectfully submit that the application is now in condition for allowance.

Nonstatutory Double Patenting Rejection

The Examiner rejected claims 23, 25-30, 33-56 and 60-65 under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-22 of U.S. Patent No. 8,895,546. Office Action dated April 21, 2017, page 2.

The Examiner provisionally rejected claims 23, 25-30, 33-51, 53-56, and 60-65 under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 20, 22-24, 27-36, 40-45 and 48-54 of co-pending Application No. 12/413,439.

The Examiner provisionally rejected claims 23, 25-30, 33-51, 53-56, and 60-65 under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 66-84 of co-pending Application No. 15/470,498.

Without conceding the basis for these rejections, Applicant E-filed terminal disclaimers to U.S. 8,895,546 and U.S. Application Nos. 12/413,439 and 15/470,498. Those terminal disclaimers were approved the same date. As the filing of a terminal disclaimer normally obviates a double patenting rejection, Applicant requests withdrawal of the rejections.

CONCLUSION

Applicants submit that the application is in condition for allowance and respectfully request the Examiner to expedite allowance of this patent application. Should the Examiner have any questions, Applicant encourages the Examiner to telephone the undersigned at 858-350-2332.

The Commissioner is hereby authorized to charge any additional fees that may be required, or credit any overpayment, including petition fees and extension of time fees, to Deposit Account No. 23-2415 (Attorney Docket No. 35401-716.301).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI
Professional Corporation

Date: April 28, 2017

By: /Matthew V. Grumbling/

Matthew V. Grumbling.
Reg. No. 44,427

Kathryn Grey
Reg. No. 69,591

650 Page Mill Road
Palo Alto, CA 94304
Direct Dial: (858) 350-2332
Customer No. 021971

Electronic Acknowledgement Receipt

EFS ID:	29068661
Application Number:	14527613
International Application Number:	
Confirmation Number:	2149
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Customer Number:	21971
Filer:	Matthew Virgil Grumbling/Lori Ford
Filer Authorized By:	Matthew Virgil Grumbling
Attorney Docket Number:	35401-716.301
Receipt Date:	28-APR-2017
Filing Date:	29-OCT-2014
Time Stamp:	18:07:15
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Response After Final Action	35401_716_301_Response_AF.pdf	29242 8b9b2a56f3b914dd6317054adc0b4295e8fa623e	no	3

Warnings:

Information:	
Total Files Size (in bytes):	29242

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/AIA/01 (06-12)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT International application number 14/527,613 filed on 10/29/2014.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Steve Cartt Date (Optional): _____

Signature: _____

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

PTO/AIA/01 (06-12)
Approved for use through 01/31/2014. OMB 0651-0032
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Title of Invention	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

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LEGAL NAME OF INVENTOR

Inventor: David Medeiros Date (Optional): 04/27/2017

Signature: [signature]

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

PTO/AIA/01 (06-12)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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Title of invention	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

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LEGAL NAME OF INVENTOR

Inventor: Garry Thomas Gwozdz Date (Optional): 27-APR-2017

Signature: _____

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

PTO/AIA/01 (06-12)
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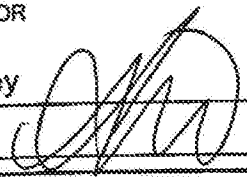
LEGAL NAME OF INVENTOR

Inventor: Andrew Loxley Date (Optional): May 12 2017

Signature: 

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LEGAL NAME OF INVENTOR

Inventor: Mark Mitchnick Date (Optional): 5/1/17

Signature: Mark Mitchnick

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

PTO/AIA/01 (06-12)
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LEGAL NAME OF INVENTOR

Inventor: David Hale Date (Optional): 4/24/13

Signature: David Hale

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

PTO/AIA/01 (06-12)
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LEGAL NAME OF INVENTOR

Inventor: Edward T. Maggio Date (Optional) :

Signature: Edward T. Maggio

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

Electronic Acknowledgement Receipt

EFS ID:	29197428
Application Number:	14527613
International Application Number:	
Confirmation Number:	2149
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Customer Number:	21971
Filer:	Matthew Virgil Grumbling/Lori Ford
Filer Authorized By:	Matthew Virgil Grumbling
Attorney Docket Number:	35401-716.301
Receipt Date:	12-MAY-2017
Filing Date:	29-OCT-2014
Time Stamp:	15:50:55
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Oath or Declaration filed	35401_716_301_Fully_Executed_Declarations.PDF	4941693 fad05ba1ea2a12b0f838bc6a1d5b4d983f975a3d	no	7

Warnings:

Information:	
Total Files Size (in bytes):	4941693

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New Applications Under 35 U.S.C. 111

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National Stage of an International Application under 35 U.S.C. 371

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New International Application Filed with the USPTO as a Receiving Office

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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

21971 7590 05/24/2017
WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

EXAMINER
MILLIGAN, ADAM C

ART UNIT	PAPER NUMBER
1612	

DATE MAILED: 05/24/2017

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/527,613	10/29/2014	Steve Cartt	35401-716.301	2149

TITLE OF INVENTION: ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0	$0	$480	08/24/2017

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

21971 7590 05/24/2017
WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/527,613	10/29/2014	Steve Cartt	35401-716.301	2149

TITLE OF INVENTION: ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

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nonprovisional	SMALL	$480	$0	$0	$480	08/24/2017

EXAMINER	ART UNIT	CLASS-SUBCLASS
MILLIGAN, ADAM C	1612	514-221000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:
- ❑ Issue Fee
- ❑ Publication Fee (No small entity discount permitted)
- ❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ❑ A check is enclosed.
- ❑ Payment by credit card. Form PTO-2038 is attached.
- ❑ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ❑ Applicant certifying micro entity status. See 37 CFR 1.29 — NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
- ❑ Applicant asserting small entity status. See 37 CFR 1.27 — NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- ❑ Applicant changing to regular undiscounted fee status. — NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
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14/527,613	10/29/2014	Steve Cartt	35401-716.301	2149

21971 7590 05/24/2017

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EXAMINER	
MILLIGAN, ADAM C	
ART UNIT	PAPER NUMBER
1612	

DATE MAILED: 05/24/2017

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 14/527,613	Applicant(s) CARTT ET AL.	
	Examiner ADAM C. MILLIGAN	Art Unit 1612	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *Applicants response and TD filed 4/28/2017*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *23,25-30,33-51,53-56,60-65*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:
   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
5. ☒ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☒ Other *BIB.DATA & A.NE*.

/ADAM C MILLIGAN/
Primary Examiner, Art Unit 1612

The present application is being examined under the pre-AIA first to invent provisions.

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

The application has been amended as follows:

Claim 48, line 3, delete "may be" and replace with --is--.

Claim 61, line 3, delete "6o" and replace with --to--.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Adam Milligan, whose telephone number is (571)270-7674. The examiner can normally be reached on Mon-Fri from 9:00am to 5:00pm.

/ADAM C MILLIGAN/
Primary Examiner, Art Unit 1612

OK TO ENTER: /A.C.M/

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: Inventors: Steve Cartt, et al. Serial No.: 14/527,613 Filing Date: October 29, 2014 Title: ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS	Group Art Unit: 1612 Confirmation No.: 2149 Examiner: Adam C. Milligan Customer No.: 21971

ELECTRONICALLY FILED ON APRIL 28, 2017

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO FINAL OFFICE ACTION

Commissioner:

This paper is submitted in response to the Final Office Action dated April 21, 2017. The Commissioner is authorized to charge any additional fees which may be required to Deposit Account No. 23-2415 (Docket No. 35401-716.301).

Remarks begin on page **2**.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14527613	CARTT ET AL.
	Examiner	Art Unit
	ADAM C MILLIGAN	1612

CPC- SEARCHED		
Symbol	Date	Examiner
A61K 9/0043, 45/06, 9/008, 31/355, 31/5513, 9/08, 47/10, 47/22, 47/26	5/8/2017	AM

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
514	221	5/8/2017	AM

SEARCH NOTES		
Search Notes	Date	Examiner
PALM Inventor Search	5/8/2017	AM
EAST Search	5/8/2017	AM
NPL Search	5/8/2017	AM

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
514	221	5/8/2017	AM
A61K	9/0043, 45/06, 9/008, 31/355, 31/5513, 9/08, 47/10, 47/22, 47/26	5/8/2017	AM

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

BIB DATA SHEET

CONFIRMATION NO. 2149

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
14/527,613	10/29/2014	424	1612	35401-716.301

APPLICANTS

Hale Biopharma Ventures, LLC, Encinitas, CA;

INVENTORS

Steve Cartt, Union City, CA;
David Medeiros, South San Francisco, CA;
Garry Thomas Gwozdz, Jim Thorpe, PA;
Andrew Loxley, Residence Not Provided;
Mark Mitchnick, East Hampton, NY;
David Hale, San Diego, CA;
Edward T. Maggio, San Diego, CA;

**** CONTINUING DATA ***************************

This application is a CON of 13/495,942 06/13/2012 PAT 8895546
which is a CIP of 12/413,439 03/27/2009
which claims benefit of 61/040,558 03/28/2008
and said 13/495,942 06/13/2012
claims benefit of 61/497,017 06/14/2011
and claims benefit of 61/570,110 12/13/2011

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED **** ** SMALL ENTITY **
11/20/2014

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☑ No Verified and Acknowledged /ADAM C MILLIGAN/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		CA	5	37	1

ADDRESS

WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050
UNITED STATES

TITLE

ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

FILING FEE RECEIVED		
1480	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

BIB (Rev. 05/07).

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14527613	CARTT ET AL.
	Examiner	**Art Unit**
	ADAM C MILLIGAN	1612

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☒ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	05/09/2017								
1	23	=								
	24	-								
2	25	=								
3	26	=								
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5	28	=								
6	29	=								
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29	55	=								
30	56	=								
	57	-								
	58	-								

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CLAIM		DATE								
Final	Original	05/09/2017								
	59	-								
31	60	=								
32	61	=								
33	62	=								
34	63	=								
35	64	=								
36	65	=								

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
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CPC						
Symbol					**Type**	**Version**
A61K		9	/	0043	F	2013-01-01
A61K		45	/	06	I	2013-01-01
A61K		9	/	008	I	2013-01-01
A61K		31	/	355	I	2013-01-01
A61K		31	/	5513	I	2013-01-01
A61K		9	/	08	I	2013-01-01
A61K		47	/	10	I	2013-01-01
A61K		47	/	22	I	2013-01-01
A61K		47	/	26	I	2013-01-01
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CPC Combination Sets								
Symbol					**Type**	**Set**	**Ranking**	**Version**
A61K		31	/	355	I	1	1	2013-01-01
A61K		2300	/	00	A	1	2	2013-01-01
A61K		31	/	5513	I	2	1	2013-01-01
A61K		2300	/	00	A	2	2	2013-01-01

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	36	
/ADAM C MILLIGAN/ Primary Examiner.Art Unit 1612	05/09/2017	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
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	ADAM C MILLIGAN	1612

US ORIGINAL CLASSIFICATION		INTERNATIONAL CLASSIFICATION	
CLASS	SUBCLASS	CLAIMED	NON-CLAIMED
514	221		

CROSS REFERENCE(S)					
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)				

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	36	
/ADAM C MILLIGAN/ Primary Examiner.Art Unit 1612	05/09/2017	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

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11	36		52												
12	37	27	53												
13	38	28	54												

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 36	
/ADAM C MILLIGAN/ Primary Examiner.Art Unit 1612 (Primary Examiner)	05/09/2017 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

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CPC							
Symbol						**Type**	**Version**
A61K	/	9	/	0043		F	2013-01-01
A61K	/	45	/	06		I	2013-01-01
A61K	/	9	/	008		I	2013-01-01
A61K	/	31	/	355		I	2013-01-01
A61K	/	31	/	5513		I	2013-01-01
A61K	/	9	/	08		I	2013-01-01
A61K	/	47	/	10		I	2013-01-01
A61K	/	47	/	22		I	2013-01-01
A61K	/	47	/	26		I	2013-01-01

CPC Combination Sets								
Symbol					**Type**	**Set**	**Ranking**	**Version**
A61K	/	31	/	355	I	1	1	2013-01-01
A61K	/	2300	/	00	A	1	2	2013-01-01
A61K	/	31	/	5513	I	2	1	2013-01-01
A61K	/	2300	/	00	A	2	2	2013-01-01

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 36	
/ADAM C MILLIGAN/ Primary Examiner.Art Unit 1612 (Primary Examiner)	05/09/2017 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

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514	221		

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/ADAM C MILLIGAN/ Primary Examiner.Art Unit 1612	05/09/2017	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

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Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	23	14	39	29	55										
	24	15	40	30	56										
2	25	16	41		57										
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11	36		52												
12	37	27	53												
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/ADAM C MILLIGAN/ Primary Examiner.Art Unit 1612 (Primary Examiner)	05/09/2017 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	14/527,613
				Filing Date	October 29, 2014
				First Named Inventor	Steve Cartt
				Art Unit	1629
				Examiner Name	N/A
Sheet	1	of	14	Attorney Docket Number	35401-716.301

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.	US-2001-0042932	11/22/2001	Mathiowitz et al.	
	2.	US-2002-0110524 A1	8/15/2002	Cowan, et al.	
	3.	US-2002-0127278	09/12/2002	Kipp	
	4.	US-2002-0141971 A1	10/3/2002	Frey	
	5.	US-2002-0168402	11/14/2002	Kipp	
	6.	US-2003-0017203 A1	1/23/2003	Crotts et al.	
	7.	US-2003-0031719	02/13/2003	Kipp	
	8.	US-2003-0040497 A1	2/27/2003	Teng et al.	
	9.	US-2003-0087820 A1	5/1/2003	Young et al.	
	10.	US-2003-0100755 A1	5/29/2003	Sham et al.	
	11.	US-2003-0118547 A1	6/26/2003	Vandenberg	
	12.	US-2003-0118594 A1	6/26/2003	Nag et al.	
	13.	US-2003-0158206 A1	8/21/2003	Billotte et al.	
	14.	US-2003-0170206 A1	9/11/2003	Rasmussen et al.	
	15.	US-2003-0181411	9/25/2003	Bosch et al.	
	16.	US-2004-0115135 A1	6/17/2004	Quay	
	17.	US-2004-0126358 A1	7/1/2004	Warne et al.	
	18.	US-2004-0147473 A1	7/29/2004	Warriell, Jr.	
	19.	US-2004-0258663 A1	12/23/2004	Quay & El-Shafy	
	20.	US-2004-141923 A1	07/22/2004	Dugger et al.	
	21.	US-2005-0130260 A1	6/16/2005	Linden et al.	
	22.	US-2005-0234101 A1	10/20/2005	Stenkamp et al.	
	23.	US-2006-0045869 A1	03/02/2006	Meezan et al.	
	24.	US-2006-0046962	3/2/2006	Meezan et al.	
	25.	US-2006-0046969 A1	3/2/2006	Maggio	
	26.	US-2006-0106227 A1	5/18/2006	Reddy et al.	
	27.	US-2006-0147386 A1	07-062006	Wermling, D. P.	

Examiner Signature	/ADAM C MILLIGAN/	Date Considered	07/11/2016

**EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy* of this form with next communication to applicant. [1]Applicant's unique citation designation number (optional). [2]See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3]Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6]Applicant is to place a check mark here if English language Translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /A.C.M/

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	14/527,613
				Filing Date	October 29, 2014
				First Named Inventor	Steve Cartt
				Art Unit	1629
				Examiner Name	N/A
Sheet	2	of	14	Attorney Docket Number	35401-716.301

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	28.	US-2006-0198896	09/07/2006	Liversidge et al.	
	29.	US-2007-0298010 A1	12/27/2007	Maggio	
	30.	US-2007-0059254 A1	3/15/2007	Singh	
	31.	US-2007-0098805 A1	5/3/2007	Liversidge	
	32.	US-2008-0200418	08/21/2008	Maggio	
	33.	US-2008-0248123	10/09/2008	Swanson et al.	
	34.	US-2008-0268032 A1	10/30/2008	Maggio	
	35.	US-2008-0279784	11/13/2008	Cartt	
	36.	US-2008-0299079 A1	12/4/2008	Meezan et al.	
	37.	US-2009-0258865 A1	10/15/2009	Cartt et al.	
	38.	US-2009-0047347	2/19/2009	Maggio	
	39.	US-2009-0130216	5/21/2009	Cartt	
	40.	US-2009-0163447	06/25/2009	Maggio	
	41.	US-2009-0297619	12/03/2009	Swanson et al.	
	42.	US-2009-0304801	12/10/2009	Liversidge et al.	
	43.	US-2009-258865	10/15/2009	Cartt	
	44.	US-2010-0068209 A1	3/18/2010	Maggio, E. T.	
	45.	US-2010-0203119 A1	8/12/2010	Leane et al.	
	46.	US-2010-0209485 A1	8/19/2010	Maggio	
	47.	US-2011-0172211	07/14/2011	Back et al.	
	48.	US-2011-0257096	10/20/2011	Maggio	
	49.	US-2012-0196941	08/02/2012	Maggio	
	50.	US-2013-0065886	03/14/2013	Cartt	
	51.	US-2014-0128479 A1	05/08/2014	Maggio	
	52.	US 2014-0170220 A1	06/19/2014	Cartt	
	53.	US-3,102,116	8/27/1963	Chase et al.	
	54.	US-3,109,843	11/5/1963	Reeder et al.	
	55.	US-3,136,815	6/9/1964	Reeder et al.	

Examiner Signature	/ADAM C MILLIGAN/	Date Considered	07/11/2016

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	56.	US-3,243,427	3/29/1966	Reeder et al.	
	57.	US-3,296,249	1/13/1967	Bell	
	58.	US-3,299,053	1/17/1967	Archer et al.	
	59.	US-3,340,253	9/5/1967	Reeder et al.	
	60.	US-3,371,085	2/27/1968	Reeder et al.	
	61.	US-3,374,225	3/19/1968	Reeder et al.	
	62.	US-3,547,828	12/15/1970	Mansfield et al.	
	63.	US-3,567,710	3/2/1971	Fryer et al.	
	64.	US-3,609,145	9/28/1971	Moffett	
	65.	US-3,722,371	3/27/1973	Boyle	
	66.	US-3,849,341	11/19/1974	Lambeiti	
	67.	US-3,987,052	10/19/1976	Hester, Jr.	
	68.	US-4,280,957	7/28/1981	Walser et al.	
	69.	US-4,397,951	8/9/1983	Taki et al.	
	70.	US-4,608,278	8/26/1986	Frank et al.	
	71.	US-4,748,158	5/31/1988	Biermann et al.	
	72.	US-4,826,689	5/2/1989	Violanto et al.	
	73.	US-4,868,289	9/1/1989	Magnusson et al.	
	74.	US-4,921,838	5/1/1990	Catsimpoolas et al.	
	75.	US-4,973,465	11/27/1990	Baurain et al.	
	76.	US-4,997,454	3/5/1991	Violanto et al.	
	77.	US-5,091,188	2/25/1992	Haynes	
	78.	US-5,100,591	3/31/1992	Leclef et al.	
	79.	US-5,118,528	6/2/1992	Fessi et al.	
	80.	US-5,145,684	9/8/1992	Liversidge et al.	
	81.	US-5,182,258	1/1/1993	Chiou	
	82.	US-5,188,837	2/23/1993	Domb	
	83.	US-5,192,528	3/3/1993	Radhakrishnan et al.	

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	84.	US-5,236,707	8/17/1993	Stewart	
	85.	US-5,268,461	12/7/1993	Shoji et al.	
	86.	US-5,308,531	5/3/1994	Urfer et al.	
	87.	US-5,317,010	5/31/1994	Pang et al.	
	88.	US-5,369,095	11/29/1994	Kee et al.	
	89.	US-5,457,100	10/10/1995	Daniel	
	90.	US-5,550,220	8/27/1996	Meyer et al.	
	91.	US-5,560,932	10/1/1996	Bagchi et al.	
	92.	US-5,639,733	6/17/1997	Koike et al.	
	93.	US-5,661,130	8/26/1997	Meezan et al.	
	94.	US-5,662,883	9/2/1997	Bagchi et al.	
	95.	US-5,665,331	9/9/1997	Bagchi et al.	
	96.	US-5,716,642	2/10/1998	Bagchi et al.	
	97.	US-5,738,845	4/14/1998	Imakawa	
	98.	US-5,780,062	7/14/1998	Frank et al.	
	99.	US-5,789,375	8/4/1998	Mukae et al.	
	100.	US-5,795,896	8/18/1998	Löfroth et al.	
	101.	US-5,814,607	9/29/1998	John S. Patton	
	102.	US-5,817,634	10/1/1998	Meezan et al.	
	103.	US-5,831,089	11/3/1998	Huber	
	104.	~~US-5,849,884 (withdrawn)~~		~~Woiszwillo et al.~~	
	105.	US-5,861,510	01/19/1999	Piscipio et al.	
	106.	US-5,863,949	01/26/1999	Robinson et al.	
	107.	US-5,955,425	9/21/1999	Morley et al.	
	108.	US-5,981,719	11/9/1999	Woiszwillo et al.	
	109.	US-6,004,574	12/21/1999	Backstrom et al.	
	110.	US-6,090,925	7/18/2000	Woiszwillo et al.	
	111.	US-6,143,211	11/07/2000	Mathiowitz et al.	

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	112.	US-6,165,484	12/26/2000	Raad et al.	
	113.	US-6,193,985	02/27/2001	Sonne	
	114.	US-6,235,224	05/22/2001	Mathiowitz et al.	
	115.	US-6,254,854	7/3/2001	Edwards, et al.	
	116.	US-6,268,053	7/31/2001	Woiszwillo et al.	
	117.	US-6,316,029	11/13/2001	Jain et al.	
	118.	US-6,316,410	11/13/2001	Barbier et al.	
	119.	US-6,375,986	4/23/2002	Ryde et al.	
	120.	US-6,395,300	5/28/2002	Straub et al.	
	121.	US-6,428,814	08/06/2002	Bosch et al.	
	122.	US-6,458,387	10/1/2002	Scott et al.	
	123.	US-6,461,591	10/8/2002	Keller et al.	
	124.	US-6,482,834	11/19/2002	Spada, et al.	
	125.	US-6,495,498	12/17/2002	Niemiec et al.	
	126.	US-6,524,557	2/25/2003	Backstrom et al.	
	127.	US-6,607,784	8/19/2003	Kipp et al.	
	128.	US-6,610,271	08/26/2003	Wermeling	
	129.	US-6,616,914	09/09/2003	Ward et al.	
	130.	US-6,627,211	09/30/2003	Choi et al.	
	131.	US-6,794,357	9/21/2004	Backstrom et al.	
	132.	US-6,869,617	3/22/2005	Kipp	
	133.	US-6,884,436	4/26/2005	Kipp	
	134.	US-6,908,626	06/21/2005	Cooper et al.	
	135.	US-6,932,962	8/23/2005	Backstrom et al.	
	136.	US-6,991,785	1/31/2006	Frey	
	137.	US-7,008,920	3/7/2006	Kimura et al.	
	138.	US-7,037,528	5/2/2006	Kipp	
	139.	US-7,132,112	11/07/2006	Choi et al.	

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	140.	US-7,434,579	10/14/2008	Young et al.	
	141.	US-8,530,463	09/10/2013	Cartt	
	142.	US-8,895,546	11/25/2014	Cartt	

U.S. UNPUBLISHED PATENT APPLICATIONS

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	143.	U.S. Prov. Appl. No. 60/148,464	08/12/1999	Noe	

FOREIGN PATENT DOCUMENTS

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	144.	EP-00780386	6/25/1997	Hoffman-La Roche AG		
	145.	EP-0396777 A1	11/14/1990	OTSUKA PHARMA CO LTD		
	146.	EP-0818442	1/14/1998	Pfizer Inc.		
	147.	EP-0945485	9/29/1999	Morton Int'l., Inc.		
	148.	EP-1004578	5/31/2000	Pfizer Products Inc.		
	149.	EP-1417972 A1	5/12/2004	ELI LILLY & COMPANY		
	150.	EP-606046	7/13/1994	CIBA-GEIGY AG		
	151.	EP-931788	7/28/1999	Pfizer Limited		
	152.	JP1-151528 (English Abstract and Claims)	6/14/1989	TAIHO YAKUHN KOGYO KK		X
	153.	JP-2003-505403 (Corresponding English equivalent WO01/06987 A2)	2/12/2003	SK Corporation (US)		X
	154.	JP-2005-508939	4/7/2005	Cooper, Eugene R.		X

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		(Corresponding English equivalent WO03/030872 A2)				
	155.	JP-2007-510722 (Corresponding English equivalent WO2005-044234 A2)	4/26/2007	Elan Pharma International Ltd.		X
	156.	WO-1990-05719	5/31/1990	British Bio-Technology Ltd.		
	157.	WO-1991-019481	12/26/1991	ALLERGAN, INC.		
	158.	WO-1994-05262 A1	3/17/1994	F.H. FAUDLING & CO. LTD.		
	159.	WO-1995-000151 A1	1/5/1995	UAB RESEARCH FOUNDATION		
	160.	WO-1995-31217 A1	11/23/1995	Dumex Ltd.		
	161.	WO-1996-27583	9/12/1996	Pfizer Inc.		
	162.	WO-1996-33172	10/24/1996	Pfizer Inc.		
	163.	WO-1997-14407 A1	4/24/1997	Research Triangle Pharmaceuticals Board of Regents, U. Tx. System		
	164.	WO-1998-03516	1/29/1998	Pfizer Inc.		
	165.	WO-1998-07697	2/26/1998	Pfizer Inc.		
	166.	WO-1998-30566	7/16/1998	Pfizer Inc.		
	167.	WO-1998-33768	8/6/1998	Pfizer Products Inc.		
	168.	WO-1998-34915	8/13/1998	Pfizer Inc.		
	169.	WO-1998-34918	8/13/1998	Pfizer Inc.		
	170.	WO-1999-007675	2/18/1999	Pfizer Products Inc.		
	171.	WO-1999-29667	6/19/1999	Pfizer Limited		
	172.	WO-1999-52889	10/21/1999	Pfizer Inc.		
	173.	WO-1999-52910	10/21/1999	Pfizer Products Inc.		
	174.	WO-2000-001390 A1	01/13/2000	RECORDATI S.A. CHEMICAL AND		

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				PHARMACEUTICAL COMPANY ET AL.		
	175.	WO-2000-74681	12/14/2000	Pfizer Limited		
	176.	WO-2003-055464	07/10/2003	BESINS INTERNATIONAL BELGIQUE ET AL.		
	177.	WO-2005-018565 A2	03/03/2005	TRANSORAL PHARMACEUTICAL S, INC.		
	178.	WO-2005-044234 A2	5/19/2005	Elan Pharma		
	179.	WO-2005-089768	9/29/2005	University of Kentucky Research Foundation		
	180.	WO-2005-117830 A1	12/15/2005	Camurus AB, Swed		
	181.	WO-2006-025882 A2	3/9/2006	The UAB Research Foundation et al.		
	182.	WO-2006-055603	5/26/2006	Elan Pharma International Ltd.		
	183.	WO-2006-088894	8/24/2006	Elan Pharma International Ltd.		
	184.	WO-2006-75123 A1	7/20/2006	Comurus AB, Swed		
	185.	WO-2007-043057 A2	4/19/2007	Touitou, Elka et al.		
	186.	WO-2007-144081 A1	12/21/2007	LTS Lohmann Therapie-System		
	187.	WO-2008-027395 A2	3/6/2008	Jazz Pharmaceuticals		
	188.	WO-2009-120933 A2	10/01/2009	Particle Sciences Inc.		

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Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	14/527,613
				Filing Date	October 29, 2014
				First Named Inventor	Steve Cartt
				Art Unit	1629
				Examiner Name	N/A
Sheet	9	of	14	Attorney Docket Number	35401-716.301

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	189.	Ahsan et al., "Effects of the permeability enhancers, tetradecylmaltoside and dimethyl-β-cyclodextrin, on insulin movement across human bronchial epithelial cells", European Journal of Pharmaceutical. Sciences, 2003; 20: 27-34	
	190.	Ahsan et al., "Sucrose cocoate, a component of cosmetic preparations enhances nasal and ocular peptide absorption", Int J Pharm, 2003; 251: 195-203.	
	191.	Albert et al., "Pharmacokinetics of diphenhydramine in man", J. Pharmacokinet, Biopharm., 3(3):159-170 (1975).	
	192.	Arnold et al., "Correlation of tetradecylmaltoside induced increases in nasal peptide drug delivery with morphological changes in nasal eithelial cells", J. Pharm. Sci. 93(9):2205-2213 (2004).	
	193.	AU application 2009228093 First exam report dated July 19, 2013	
	194.	Beam et al., "Blood, Brain, Cerebrospinal Fluid Concentrations of Several Antibiotics in Rabbits with Intact and Inflamed Meninges", Antimicrobal Agents and Chemotherapy, December 1977, pp 710-716	
	195.	Bhairi S.M., "A guide to the properties and uses of detergents in biological systems", *Calbiochem,* pp. 1-42 (2001).	
	196.	Birkett et al., "Bioavailability and First Pass Clearance", Australian Prescriber, 1991, pp. 14-16, Vol. 14.	
	197.	Birkett et al., "How Drugs are Cleared by the Liver", Australian Prescriber, 1990, pp. 88-89, Vol. 13, No. 4.	
	198.	CA 2,723,470 Office action dated June 7, 2012	
	199.	Castro et al., "Ecologically safe A1kyl glucoside-based gemini surfactants", ARKIVOC, xii:253-267 (2005)	
	200.	Chavanpatil and Vavia, "Nasal drug delivery of sumatriptan succinate", Pharmazie., 2005 May:60(5):347-349.	
	201.	Chen et al., "Peptide Drug Permeation Enhancement By Select Classes of Lipids", presented ath the 45th American Society of Cell Biology, S.F., CA, December 10-14 (2005); 1 page total.	
	202.	Chen-Quay et al., "Identification of tight junction modulating lipids", J. Pharm. Sci., 98(2):606-619 (2009)	
	203.	Chiou et al., "Improvement of Systemic Absorption of Insulin Through Eyes with Absorption Enhancers", Journal of Pharmaceutical Sciences, October 1989, pp. 815-818, Vol. 78, No. 10	

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	204.	Chiou et al., "Systemic Delivery of Insulin Through Eyes to Lower the Glucose Concentration", Journal of Ocular Pharmacology, 1989, pp. 81-91, Vol. 5, No. 1.	
	205.	Chinese Patent Office from Application No. CN200980157305.0 dated January 28, 2013	
	206.	Davis and Illum, "Absorption enhancers for nasal drug delivery", Clin. Pharmacokine., 2003:42(13):107-28	
	207.	De Vry and Schreiber, "Effects of selected serotonin 5-HT(1) and 5-HT(2) receptor agonists on feeding behavior: possible mechanisms of action", Neurosci. Biobehav. Rev., 24(3):341-53 (2000)	
	208.	Definition downloaded 13 September 2012 at the medical-dictionary.thefreedictionary.com/p/encephalin	
	209.	Definition of pilus, Merriam-Webster Medical Dictionary, http://www.merriam-webster.com/medical/pilus, accessed online on 28 May 2013	
	210.	Definition of villus, Merriam-Webster Medical Dictionary, http://www.merriam-webster.com/medical/villus, accessed online on 28 May 2013	
	211.	Drewe et al., "Enteral absorption of octreotide: absorption enhancement by polyoxyethylene-24-cholesterol ether", Br. J. Pharmacol., 108(2):298-303 (1993).	
	212.	Duquesnoy et al., "Comparative clinical pharmacokinetics of single doses of sumatriptan following subcutaneous, oral, rectal and intranasal administration", Eur. J. Pharm. Sci., 6(2):99-104 (1998)	
	213.	Edwards CM., "GLP-1: target for a new class of antidiabetic agents?", J.R. Soc. Med., 97(6):270-274 (2004).	
	214.	Eley and Triumalashetty, "In vitro assessment of A1kylglycosides as permeability enhancers", AAPS PharmsciTech., 2(3): article 19, pages 1-7 (2001).	
	215.	EP application 09723906.5 Extended European search report dated June 3, 2013	
	216.	EP08747813 Supplementary Search Report dated June 2, 2010	
	217.	European Search Report (ESR) from EP 09 83 5809 dated 13 November 2012	
	218.	Fix, "Oral controlled release technology for peptides: status and future prospects", Pharmaceutical Research 1996 Dec;13(12):1760-1764.	
	219.	Fricker et al., "Permeation enhancement of octreotide by specific bile salts in rats and human subjects: in vitro, in vivo correlations", Br. J. Pharmacol., 117(1):217-23 (1996)	
	220.	Gordon et al., "Nasal Absorption of Insulin: Enhancement by Hydrophobic Bile Salts", Proceedings of the National Academy of Sciences of the United States of America, November 1985, pp. 7419-7423, Vol. 82.	

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	221.	Hathcox and Beuchat, "Inhibitory effects of sucrose fatty acid esters, A1one and in combination with ethylenediaminetetraacetic acid and other organic acids, on viability of Escherichia coli 0157:H7", Food Microbiology, Volume 13, Issue 3, 213-225 (1996).	
	222.	Hovgaard et al., "Insulin Stabilization and GI Absorption", Journal of Controlled Release, March 1992, pp. 99-108, Vol. 19, Issue 1-3.	
	223.	Hovgaard et al., "Stabilization of insulin by A1kylmaltosides. A. Spectroscopic evaluation", International Journal of Pharmaceutics, 132(1-2):107-113 (1996).	
	224.	Hovgaard et al., "Stabilization of Insulin by A1kylmaltosides. B. Oral Absorption in Vivo in Rats", International Journal of Pharmaceutics, 1996, pp. 115-121, Vol 132.	
	225.	Hussain et A1, "Absorption enhancers in pulmonary protein delivery." J Control Release. 2004 Jan 8;94(1):15-24.	
	226.	International Search Report (ISR) from PCT/US2011/056735 dated June 22, 2012	
	227.	JP2010-507633 Office Action dated October 23, 2012	
	228.	JP2010-507633 Decision of refusal dated July 9, 2013	
	229.	Katzung, B., "Basic and Clinical Pharmacology, 7th Edition", Appleton & Lange: Stamford, Connecticut, 1998, pp. 34-49	
	230.	Kissel et al., "Tolerability and absorption enhancement of intranasally administered octreotide by sodium taurodihydrofusidate in healthy subjects." Pharm Res. 1992 Jan;9(1):52-57.	
	231.	Kite et al., "Use of in vivo-generated biofilms from hemodialysis catheters to test the efficacy of a novel antimicrobial catheter lock for biofilm eradication in vitro." J Clin Microbiol. 2004 Jul;42(7):3073-3076.	
	232.	Lacy, C, et al., "Drug Information Handbook, 7th Edition 1999-2000" Lexi-Comp, Inc., 1999, pp. 163-164.	
	233.	Lahat et al., "Intranasal midazolam for childhood seizures", The Lancet, 1998; 352: 620	
	234.	Lehninger et al., "Principles of Biochemistry with an Extended Discussion of Oxygen-Binding Proteins", 1982, pp. 150-151, Worth Publishers, Inc.	
	235.	Liu et al., "Interaction between chitosan and A1kyl P-D-glucopyranoside and its effect on their antimicrobial activity", Carbohydrate Polymers. 2004; 56: 243-250.	
	236.	Maa and Prestrelski, "Biopharmaceutical powders: particle formation and formulation considerations", Curr. Pharm. Biotechnol., 1(3):283-302 (2000).	
	237.	Material Safety Data Sheet for Anatrace, Inc. product n-DODECYL-β-d-MALTOPYRANOSIDE, ANAGRADE, Dated: 01/25/1994 and Revised: 07/15/2004,	

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		hhtp://media.affymetrix.com/estore/browse/level_three)category_ and_products.jsp?category=35843&categoryldClicked=35843&expand=true&parent=35 900, access online on 13 December 2012	
	238.	Mathew N.T., "Serotonin 1D (5-HT1D) agonists and other agents in acute migraine", Neurol. Clin., 15(1):61-83 (1997).	
	239.	Matsumura et al., "Surface activities, biodegradability and antimicrobial properties of n-alkyl glucosides, mannosides and galactosides", Journal of the America Oil Chemists' Society, 67(12):996-1001 (1990)	
	240.	Moses et al., "Insulin Administered Intranasally as an Insulin-Bite Salt Aerosol - Effectiveness and Reproducibility in Normal and Diabetic Subjects", Diabetes, November 1983, pp. 1040-1047, Vol. 32.	
	241.	Murakami et al., "Assessment of Enhancing AbititY of Medium-Chain A1kyl Saccharides as New Absorption Enhancers in Rat Rectum", International Journal of Pharmaceutics, February 1992, pp. 159-169, Vol. 79, Issue 1-3]	
	242.	Ogiso et al., "Percutaneous Absorption of Elcatonin Chemical and Hypocalcemic Effect in Rat", Chemical & Pharmaceutical Bulletin, February 1991, pp. 449-453, Vol. 39, Issue 2, The Pharmaceutical Society of Japan, Tokyo, Japan.	
	243.	Olesen et al., "The Headaches", *Lippincott Williams & Wilkins,* page 474 (2005)	
	244.	Paulsson and Edsman, "Controlled drug release from Gels using surfactant aggregates. II Vesicles formed from mixtures of amphiphilic drugs and oppositely charged surfactants", Pharm, Res., 18(11):1586-1592 (2001).	
	245.	PCT/US08/62961 Search Report dated 7/25/08	
	246.	PCT/US08/62961 International Preliminary Report on Patentability dated 11/10/2009	
	247.	PCT/US09/38696 Search Report dated 9/28/09	
	248.	PCT/US09/38696 International Preliminary Report on Patentability dated 9/28/2010	
	249.	PCT/US2012/042311 Search Report dated 08/31/2012	
	250.	Phillips, A., "The challenge of gene therapy and DNA delivery", J. Pharm Pharmacology 53: 1169-1174, 2001	
	251.	Pillion et al., "Synthetic long-chain A1kyl maltosides and A1kyl sucrose esters as enhancers of nasal insulin absorption", J. Pharm. Sci., 91:1456-1462 (2002).	
	252.	Pillion et al., "Systemic Absorption of Insulin Delivered Topically to the Rat Eye",	

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		Investigative Ophthalmology & Visual Science, November 1991, pp. 3021-3027, Vol. 32, Issue 12.	
	253.	Pirollo et al., "Targeted Delivery of Small Interfering RNA: Approaching Effective Cancer Therapies", Cancer Res. 68(5): 1247-1250, 2008	
	254.	Richards R.M., "Inactivation of resistant Pseudomonas aeruginosa by antibacterial combinations", J. Pharm. Pharmacol., 23:136S-140S (1971)	
	255.	Salzman et al., "Intranasal Aerosolized Insulin", The New England Journal of Medicine, April 25, 1985, pp. 1078-1084, Vol. 312, Issue 17	
	256.	Sanders et al., "Pharmacokinetics of ergotamine in healthy volunteers following oral and rectal dosing", Eur. J. Clin. Pharmacol., 30(3):331-334 (1986).	
	257.	Shim and Kim, "Administration Route Dependent Bioavailability of Interferon-α and Effect of Bile Salts on the Nasal Absorption", Drug Development and Industrial Pharmacy, 19(10):1183-1199 (1993).	
	258.	Stevens and Guillet, "Use of Glucagon to Treat Neonatal Low-Output Congestive Heart Failure after Maternal Labetalol Therapy", The Journal of Pediatrics, July 1995, pp. 151-153, Volume 127, Issue 1.	
	259.	Swarbrick et al., Encyclopedia of Pharmaceutical Technology, Informa Health Care, 2nd edition, Vol. 1, page 918 (2002).	
	260.	Tsuchido et A1,, "Lysis of Bacillus subtilis Cells by Glycerol and Sucrose Esters of Fatty Acids", Applied and Environmental Microbiology. Vol. 53, No.3, 505-508, 1987.	
	261.	Türker et al., "Nasal route and drug delivery systems", Pharm. World Sci., 26(3):137-42 (2004).	
	262.	Turton et al., "A role for glucagon-like peptide-1 in the central regulation of feeding", Nature, 1996; 379:69-72	
	263.	U.S. Serial No. 12/116,842 Office action mailed May 25, 2011	
	264.	U.S. Serial No. 12/116,842 Office action mailed April 2, 2013	
	265.	U.S. Serial No. 12/116,842 Office action mailed November 15, 2011	
	266.	U.S. Serial No. 12/116,842 Office action mailed December 17, 2013	
	267.	U.S. Serial No. 12/266,529 Office action mailed July 10, 2012	
	268.	U.S. Serial No. 12/266,529 Office action mailed November 16, 2011	
	269.	U.S. Serial No. 12/413,439 Office action mailed March 18, 2011	

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	270.	U.S. Serial No. 12/413,439 Office action mailed November 21, 2011	
	271.	U.S. Serial No. 12/413,439 Office action mailed June 19, 2014	
	272.	U.S. Serial No. 13/495,942 Office Action mailed October 1, 2013	NP
	273.	Vidal et al., "Making sense of antisense", European Journal of Cancer, 41:2812-2818, 2005	
	274.	Watanabe et al., "Antibacterial Carbohydrate Monoesters Suppressing Cell Growth of Streptoccus mutans in the Presence of Sucrose", Current Microbiology, September 2000, pp. 210-213, Vol. 41, No. 3.	
	275.	Weber and Benning, "Metabolism of orally administered A1kyl beta-glycosides in the mouse", J. Nutr., 114:247-254 (1984).	
	276.	Webpage for Anatrace products of Affymetrix, http://www.affymetrix.com/estore/browse/level_three_category_and_products.jsp?category=35843&categoryIdClicked=35843&expand=true&parent=35900, accessed online on 13 December 2012	
	277.	WERMELING et al., "Pharmacokinetics and pharmacodynamics of a new intranasal midazolam formulation in healthy volunteers," Anesthesia & Analgesia 103(2):344-349 (2006)	
	278.	Yamamoto et al., "The Ocular Route for Systemic Insulin Delivery in the A1bino Rabbit", The Journal of Pharmacology and Experimental Therapeutics, April 1989, pp. 249-255, Vol. 249; No. 1.	
	279.	Yu Xinrui et al., "Triptan Medicament and Migraine", World Pharmacy (Synthetic Drug and Biochemical Drug Formulation Fascicule), 22(2):91-92 (2001)	

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/527,613	10/29/2014	Steve Cartt	35401-716.301	2149

21971 7590 06/14/2017

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PALO ALTO, CA 94304-1050

EXAMINER
MILLIGAN, ADAM C

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
06/14/2017	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@wsgr.com

Corrected Notice of Allowability	Application No. 14/527,613	Applicant(s) CARTT ET AL.	
	Examiner ADAM C. MILLIGAN	Art Unit 1612	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *Applicants response and TD filed 4/28/2017*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *23,25-30,33-51,53-56,60-65*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:
   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 14pp(7/14/2016)
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
5. ☒ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/ADAM C MILLIGAN/
Primary Examiner, Art Unit 1612

The present application is being examined under the pre-AIA first to invent provisions.

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

The application has been amended as follows:

Claim 48, line 3, delete "may be" and replace with --is--.

Claim 50, line 1, delete "claim 24" and replace with --claim 49--.

Claim 61, line 3, delete "6o" and replace with --to--.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Adam Milligan, whose telephone number is (571)270-7674. The examiner can normally be reached on Mon-Fri from 9:00am to 5:00pm.

/ADAM C MILLIGAN/
Primary Examiner, Art Unit 1612

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

21971 7590 05/24/2017
WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/527,613	10/29/2014	Steve Cartt	35401-716.301	2149

TITLE OF INVENTION: ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0	$0	$480	08/24/2017

EXAMINER	ART UNIT	CLASS-SUBCLASS
MILLIGAN, ADAM C	1612	514-221000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Wilson Sonsini Goodrich & Rosati
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: Hale Biopharma Ventures, LLC

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Encinitas, CA 92024

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:
- ☒ Issue Fee
- ☐ Publication Fee (No small entity discount permitted)
- ☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ☐ A check is enclosed.
- ☐ Payment by credit card. Form PTO-2038 is attached.
- ☒ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number 232415 (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ☐ Applicant certifying micro entity status. See 37 CFR 1.29
- ☐ Applicant asserting small entity status. See 37 CFR 1.27
- ☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date 2017-08-16

Typed or printed name Raj Advani Registration No. 52,543

Electronic Patent Application Fee Transmittal

Application Number:	14527613
Filing Date:	29-Oct-2014
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Filer:	Raj J. Advani/diane garcia
Attorney Docket Number:	35401-716.301

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
UTILITY APPL ISSUE FEE	2501	1	480	480

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**480**

Electronic Acknowledgement Receipt

EFS ID:	30100371
Application Number:	14527613
International Application Number:	
Confirmation Number:	2149
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Customer Number:	21971
Filer:	Raj J. Advani/diane garcia
Filer Authorized By:	Raj J. Advani
Attorney Docket Number:	35401-716.301
Receipt Date:	16-AUG-2017
Filing Date:	29-OCT-2014
Time Stamp:	17:39:12
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$480
RAM confirmation Number	081717INTEFSW00004372232415
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	35401-716-301.pdf	121115 8f3f8faafdb9b2dc9df7c399c88bff05f78361f8	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30490 ba239f02a97d0055ba7ced2bd795334fdd984c7b	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	151605		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/527,613	09/19/2017	9763876	35401-716.301	2149

21971 7590 08/30/2017

WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 17 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

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Hale Biopharma Ventures, LLC, Encinitas, CA;
David Medeiros, South San Francisco, CA;
Garry Thomas Gwozdz, Jim Thorpe, PA;
Andrew Loxley, Residence Not Provided;
Mark Mitchnick, East Hampton, NY;
David Hale, San Diego, CA;
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