FORMULATIONS COMPRISING SELETRACETAM AND METHODS OF USE

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 63/573,548, filed April 3, 2024, the contents of which are fully incorporated by reference herein.

BACKGROUND

Epilepsy is a chronic disorder of the brain characterized by spontaneous recurrent seizures. Approximately 70 million people worldwide have epilepsy, making it one of the most common neurological diseases globally [Devinsky et al., *Epilepsy*, Nature Review: Disease Primers May 3, 2018; Ngugi, Anthony K., et al., Epilepsia 51 (5) (2010): 883-890; Guekht, Alla, et al., Epilepsia 62(5) (2021): 1057-1063]. Approximately 35% of epilepsy patients do not respond to currently available antiseizure medications and have uncontrolled (drug resistant) epilepsy (DRE) [Chen, Zhibin, et al., JAMA neurology 75 (3) (2018): 279-286; Löscher, Wolfgang, and Pavel Klein, CNS drugs 35 (9) (2021): 935-963]. Uncontrolled epilepsy can severely impact a patient's life. Seizures often lead to physical injuries, including (but not limited to) head injuries, fractures, cuts, and bruises, and are at times lethal. Patients with epilepsy have a higher mortality rate compared to the general population, with uncontrolled seizures corresponding to a mortality risk of 1% per year of life [Thurman, David J., et al., Epilepsia 58(1) (2017): 17-26].

Further, some patients with uncontrolled epilepsy have acutely repeating seizures, termed acute repetitive seizures (ARS) or cluster seizures. Uncontrolled seizures may also arise in patients suffering temporarily from other diseases such as infections (e.g., a common flu) or any other disease, which impacts overall well-being and thus may result in increased seizure risks. ARS or cluster seizures are defined variably as more than 1 seizure during a short period of time, typically within 24-48 hours of the first seizure. The proportion of patients with epilepsy who have ARS has been variably estimated to range from 5-~70% of all patients with uncontrolled epilepsy [Gidal, Barry, Pavel Klein, and Lawrence J. Hirsch, Epilepsy & Behavior 112 (2020): 107391; Jafarpour, Saba, et al., Pediatric neurology 137 (2022): 22-29]. Patients with ARS have

worse epilepsy, and further increase in the risk of bad outcomes, including (but not limited to) injury, psychiatric and cognitive comorbidities, emergency room visits, hospital admissions, status epilepticus, and early death [Chung, Steve, et al., Epilepsy Research 177 (2021): 106748]. In addition, uncontrolled epilepsy and ARS often adversely affect quality of life. Epilepsy or seizures often lead to loss of independence, ability to drive, job or educational opportunities, and strained personal relationships [Penovich, Patricia E., et al., The neurologist 22.6 (2017): 207-214). Accordingly, there is an ongoing need for compositions and methods for treating epilepsy or ARS.

SUMMARY

In certain aspects, provided herein is a method of treating a seizure disorder in a subject in need thereof comprising administering seletracetam to the subject intranasally, buccally, or sublingually.

In certain aspects, provided herein is a method of administering seletracetam to a subject comprising administering seletracetam to the subject intranasally, buccally, or sublingually.

In certain aspects, provided herein is a method of stabilizing the progression of a focal onset seizure with retained awareness in a subject in need thereof comprising administering seletracetam to the subject intranasally, buccally, or sublingually.

In certain aspects, provided herein is a method of terminating a seizure in a subject in need thereof comprising administering seletracetam to the subject intranasally, buccally, or sublingually.

In certain aspects, provided herein is a method of treating a pain in a subject in need thereof comprising administering seletracetam to the subject intranasally, buccally, or sublingually.

In certain aspects, provided herein is a method of treating a neurological or psychiatric disorder in a subject in need thereof comprising administering seletracetam to the subject intranasally, buccally, or sublingually.

In certain aspects, provided herein is a pharmaceutical formulation comprising seletracetam and a pharmaceutically acceptable liquid carrier.

In certain aspects, provided herein is a nasal spray device comprising seletracetam.

In certain aspects, provided herein is an oromucosal spray device comprising seletracetam.

In certain aspects, provided herein is an orally disintegrating tablet comprising seletracetam.

In certain aspects, provided herein is a mucoadhesive film comprising seletracetam.

DETAILED DESCRIPTION

A significant subset of epilepsy patients experience focal seizures with retained awareness or a seizure aura, which is a sensation that precedes the onset of a full seizure. Patients with auras may develop a full focal seizure with impaired awareness or a generalized seizure shortly after the onset of the aura, providing a window of awareness. In a population-based study, 31% of the total sample (n=1897) and 39% of those with active epilepsy (n=765) reported experiencing an aura. Six percent of these individuals reported more than one type of aura. Non-specified auras were the most frequently reported (35%), followed by somatosensory (11%) and vertiginous (11%) auras. While the majority of those reporting auras had focal epilepsies (59%), auras of a mostly non-specific nature were also experienced by 13% of those with generalized epilepsies. [Nakken, K. O., et al. "The occurrence and characteristics of auras in a large epilepsy cohort." Acta Neurologica Scandinavica 119.2 (2009): 88-93]. Focal seizures with retained awareness often progress into focal seizures with impaired awareness or bilateral tonic-clonic seizures, previously known as secondarily generalized seizures. These patients may be on chronic antiseizure medication but still experience breakthrough seizures, indicating treatment resistance. Other patients may not be on chronic antiseizure medication due to infrequent seizures, adverse effects, or non-adherence. Notably, a CDC report indicated that of the 2.6 million patients in the US who self-reported having an active seizure disorder or epilepsy, only 90% reported taking antiseizure medication regularly. Morbidity and Mortality Weekly Report, Vol. 67, No. 15 (April 20, 2018).

Additionally, epilepsy patients may be able to anticipate a seizure in situations where they are equipped with seizure detection devices, or when they are at higher risk for seizures under specific conditions such as when they are sleep deprived, experience stress, experience hormone changes during their menstrual cycle, have taken a recreational drug, experience drug withdrawal, experience a febrile illness, or have missed or taken an incorrect dosage of their chronic antiseizure medication. Further, patients with reflex epilepsy may be able to anticipate a

seizure when exposed to a known seizure trigger such as changing light (for patients with photic epilepsy), reading (for patients with reading epilepsy), or specific sounds (for patients with audiogenic or sound-induced epilepsy).

In these and other scenarios where seizures are anticipated or have already commenced with retained awareness, acute administration of rescue medication could prevent or terminate the seizure or inhibit its progression from a seizure with awareness to one without awareness, or to a bilateral tonic-clonic seizure (which manifests as a convulsion). For patients experiencing prolonged seizures, the rescue treatment may terminate the seizure—a type of treatment known as rapid epileptic seizure termination (REST). For patients with reflex epilepsy or triggered seizures in the setting of sleep deprivation, stress, menstrual cycle changes, alcohol or other drug use, fever or temporary lack of access to chronic antiseizure medications, rescue treatment may prevent the occurrence of a seizure. Accordingly, there is a need for rescue treatment compositions and methods for both patients on chronic antiseizure medication who experience breakthrough seizures and those who are untreated and require rescue treatment on an as-needed basis.

Seizure rescue treatments must be fast-acting, which typically restricts them to intravenous (IV) treatments and rapidly absorbed non-IV treatments, such as those administered rectally, nasally, buccally, or sublingually. Given that most situations necessitating rescue treatment occur outside of hospital or emergency room settings where IV treatment is accessible, medications administered nasally, buccally, sublingually, or rectally become the primary options for such interventions.

Epilepsy patients with ARS typically receive treatment with chronic antiseizure medication for epilepsy and additional treatment for ARS. ARS treatment consists of acutely administered medications that act on the brain quickly to prevent further seizures during the ARS at risk period and, if possible, stop ongoing seizures [Blond, Benjamin N., and Lawrence J. Hirsch, Expert Review of Neurotherapeutics 22(7) (2022): 567-577]. The need for administration of quickly acting treatment limits ARS treatment options to intravenous (IV) treatment and rapidly absorbed non-IV treatment such as rectally, nasally, buccally, or sublingually administered medications. Because most ARS occurs outside of settings where IV treatment is an option, i.e. hospital or emergency rooms, nasally, buccally, sublingually, or rectally administered medications are the mainstay of ARS treatment.

The only class of antiseizure medications that have been successfully formulated for non-oral and non-IV administration such as rectal, intranasal, buccal, or sublingual administration are benzodiazepines, a class of medications that act on the GABA-A receptor, the chief brain mediator of neural inhibition [Blond, Benjamin N., and Lawrence J. Hirsch, Expert Review of Neurotherapeutics 22.7 (2022): 567-577]. All currently available ARS treatments include benzodiazepines: intranasal midazolam; intranasal, buccal, and rectal diazepam; and sublingual lorazepam and clonazepam are the mainstay of ARS treatment in outpatient settings. Likewise, only benzodiazepines are approved or under advanced development for REST treatment, including Staccato® alprazolam, Zeneo® midazolam, and midazolam intramuscular autoinjector [Asnis-Alibozek, A., & Detyniecki, K. (2021). The unmet need for rapid epileptic seizure termination (REST). Epilepsy & behavior reports, 15, 100409].

While generally considered effective in ARS and for REST treatment, acutely administered benzodiazepines have the potential for severe side effects that limit their usefulness and restrict their repeated use. These include respiratory depression, a complication that can lead to intubation, ICU admission and death, and sedation, which may limit the ability to act independently for the duration of the medications' effect. These side effects are often aggravated by other co-medications. Especially the co-medication of opioids can result in severe, potentially fatal respiratory depression. Benzodiazepines also have the potential for abuse and addiction, including dependency. For these reasons, the FDA has restricted the use of benzodiazepines approved for ARS rescue treatment to no more than 1 episode every three (intranasal midazolam) or five (intranasal and rectal diazepam) days and no more than 5 episodes per month.

The use of benzodiazepines for the treatment of epilepsy is also hampered by the fact that diverse mutations of the gamma-amino butyric acid A ($GABA_A$) receptor exist, which render this receptor insensitive or less sensitive to drugs acting on this receptor. Such $GABA_A$ receptor mutations are the cause of different forms of genetic epilepsy syndromes. A problem for treating seizures and seizure clusters in such syndromes is that the mutations render benzodiazepine receptor targeting antiseizure medications and also benzodiazepine receptor targeting rescue medications such as midazolam or diazepam ineffective or less effective, with a more than 25% reduced sensitivity to benzodiazepines. Frequent use of benzodiazepine treatment may also result in a loss of efficacy due to the "habituation" effect.

Seletracetam is a non-benzodiazepine antiseizure medication tested in animal models of epilepsy and in phase 1 and 2a human studies in healthy volunteers and patients with epilepsy. Seletracetam does not form salts but does form ionic co-crystals involving metal halides in combination with seletracetam. In addition to halides (including, but not limited to calcium chloride, magnesium chloride and lithium chloride), co-crystals can be also formed between seletracetam and organic acids. Various co-crystals of seletracetam are described by Braga et al, and by Wouters et al, which are incorporated by reference [Braga, D., et al. (2018), CrystEngComm, 20(16), 2212-2220; Wouters, J. et al, (2013), CrystEngComm, 15(44), 8898-8902]. Co-crystals of seletracetam, while not being salts as such, present distinct solid crystal structures with distinct physicochemical properties such as crystal structure, melting point, or solubility, differentiating them from pure seletracetam, while the chemical structure of seletracetam is not affected by such co-crystal formation.

Seletracetam's antiseizure action is mediated by its modulation of the synaptic vesicle 2A (SV2A) protein's effect on neurotransmitter release. It has no impact on GABA-A-gated currents [RIGO, J. M., et al., In: Epilepsia. 9600 GARSINGTON RD, OXFORD OX4 2DQ, OXON, ENGLAND: BLACKWELL PUBLISHING, 2005. Page. 110-111; US patent no. 6,806,287]. Seletracetam could also be effective in the treatment of migraine, neuralgia, chronic pain, peripheral nerve pain, and neuropathic pain. Furthermore, seletracetam is expected to be also active in other CNS conditions including (but not limited to) bipolar disorders, mania, depression, anxiety, cerebral ischemia, essential tremor, neonatal cerebral hemorrhage, amyotrophic lateral sclerosis, spasticity, and Parkinson's disease, if administered at a therapeutic dose. Pharmacological effects of seletracetam are described, for example, in US Patent No. 6,806,287, which is incorporated by reference herein.

Seletracetam in orally administered doses of 2-600 mg daily dose administered as single or multiple dose was safe and well tolerated in phase 1 and 2a studies in single and multiple rising dose studies in healthy volunteers and in patients with epilepsy [LEESE, P. T., et al., In: EPILEPSIA. 9600 GARSINGTON RD, OXFORD OX4 2DQ, OXON, ENGLAND: BLACKWELL PUBLISHING, 2006. pages 164-164 Abstract no. 2.131.; TRENITE, D., et al., In: Epilepsia. COMMERCE PLACE, 350 MAIN ST, MALDEN 02148, MA USA: WILEY-BLACKWELL PUBLISHING, INC, 2006. pages. 161-162, abstract no. 2.123]. In patients with epilepsy and epileptiform response to intermittent photic stimulation (IPS), a condition

commonly used for human proof of concept efficacy and tolerability studies of antiseizure medications, seletracetam effectively suppressed IPS at single orally administered doses of 0.5-20 mg, with maximum efficacy at 10 mg dose [TRENITE, D., et al., In: Epilepsia. COMMERCE PLACE, 350 MAIN ST, MALDEN 02148, MA USA: WILEY-BLACKWELL PUBLISHING, INC, 2006. pages. 161-162, abstract no. 2.123] with good tolerability. [Trenite, DKN., Stockis, A., Hirsch, E., Genton, P., Abou-Khalil, BW., French, J., Masnou, P., and Löscher, W.: A multicenter Phase II randomized, placebo-controlled single-blind trial with the SV2A ligand seletracetam in photosensitive epilepsy patients. Epilepsy & Behavior 164 (2025) 110241]

In preferred aspects, provided is a method of treating a seizure disorder in a subject in need thereof comprising administering seletracetam to the subject intranasally, buccally, or sublingually. In preferred embodiments, the seletracetam is administered intranasally. In some embodiments, the seletracetam is administered buccally or sublingually. In certain embodiments, the seletracetam is administered buccally. In some embodiments, the seletracetam is administered sublingually. In some embodiments, the seizure disorder comprises epilepsy, a first seizure, a febrile seizure, or eclampsia. In preferred embodiments, the seizure disorder comprises epilepsy. In some embodiments, the epilepsy comprises focal onset epilepsy with retained awareness, absence epilepsy, frontal lobe epilepsy, temporal lobe epilepsy, neocortical epilepsy, juvenile myoclonic epilepsy, epilepsy with aura, reflex epilepsy, catamenial epilepsy, epilepsy without aura, focal onset epilepsy without retained awareness, Lennox-Gastaut syndrome, infantile spasms, childhood absence epilepsy, Rasmussen's encephalitis, Dravet syndrome, tuberose sclerosis complex, hypothalamic hamartoma, or developmental and epileptic encephalopathy. In preferred embodiments, the epilepsy comprises epilepsy with aura or focal onset epilepsy with retained awareness. In more preferred embodiments, the epilepsy comprises focal onset epilepsy with retained awareness.

In certain embodiments, the epilepsy comprises reflex epilepsy. In some embodiments, the reflex epilepsy comprises photic epilepsy, reading epilepsy, or audiogenic epilepsy.

In some embodiments, the subject is experiencing a seizure, a seizure cluster, an aura, or a prodrome. In certain embodiments, the subject is experiencing a seizure or a seizure cluster. In preferred embodiments, the subject is experiencing a seizure. In certain embodiments, the subject is experiencing a seizure cluster. In some embodiments, the subject is experiencing an aura or a prodrome. In certain embodiments, the subject is experiencing an aura. In some embodiments,

the subject is experiencing a prodrome. In some embodiments, the seizure is an acute seizure, a seizure with aura or prodrome, a reflex seizure, a catamenial seizure, a focal onset seizure with retained awareness, a secondarily generalized seizure with focal onset, an absence seizure, a myoclonic seizure, a tonic seizure, an atonic seizure, a clonic seizure, a tonic-clonic seizure, an epileptic spasm, a focal seizure with or without altered awareness, a focal onset seizure without retained awareness, a status epilepticus, a subclinical seizure, or an electrographic seizure. In certain embodiments, the subject is experiencing the seizure cluster. In other embodiments, the subject is experiencing seizures which are subclinical or electrographic seizures. In preferred embodiments, the seizure comprises a seizure with aura or prodrome, a focal onset seizure with retained awareness, or a reflex seizure. In more preferred embodiments, the seizure comprises a focal onset seizure with retained awareness.

In certain embodiments, the seizure is triggered by sleep deprivation, stress, hormone changes during the menstrual cycle, drug use, drug withdrawal, a febrile illness, or a missed or incorrect dosage of chronic antiseizure medication.

In some embodiments, the seizure is triggered by sleep deprivation. In certain embodiments, the seizure is triggered by stress.

In some embodiments, the seizure is triggered by hormone changes during the menstrual cycle. In certain embodiments, the seizure is triggered by a drop in progesterone.

In certain embodiments, the seizure is triggered by drug use or drug withdrawal. In some embodiments, the seizure is triggered by alcohol use, alcohol withdrawal, cocaine use, cocaine withdrawal, amphetamine use, amphetamine withdrawal, methamphetamine use, methamphetamine withdrawal, heroin use, heroin withdrawal, phencyclidine use, phencyclidine withdrawal, cannabis use, cannabis withdrawal, MDMA use, or MDMA withdrawal.

In some embodiments, the seizure is triggered by a febrile illness. In certain embodiments, the febrile illness is caused by a bacterial infection, a viral infection, a parasite infection, an autoimmune disorder, or a heat stroke.

In certain embodiments, the seizure is triggered by a missed or incorrect dosage of chronic antiseizure medication. In some embodiments, the seizure is triggered by an incorrect dosage of chronic antiseizure medication. In certain embodiments, the seizure is triggered by at least one missed dose, at least two consecutive missed doses, or at least three consecutive missed doses of chronic antiseizure medication.

In certain embodiments, the seizure is a reflex seizure. In some embodiments, the seizure is a reflex seizure triggered by light, reading, or sound. In certain embodiments, the seizure is a reflex seizure triggered by light. In some embodiments, the seizure is a reflex seizure triggered by sound. In certain embodiments, the seizure is a reflex seizure triggered by reading.

In certain embodiments, the subject identifies that they are experiencing a seizure, a seizure cluster, an aura, or a prodrome; and the subject administers the seletracetam. In some embodiments, the subject identifies that they are experiencing a seizure or a seizure cluster; and the subject administers the seletracetam. In preferred embodiments, the subject identifies that they are experiencing a seizure; and the subject administers the seletracetam. In some embodiments, the subject identifies that they are experiencing a seizure cluster; and the subject administers the seletracetam. In certain embodiments, the subject identifies that they are experiencing an aura or a prodrome; and the subject administers the seletracetam. In some embodiments, the subject identifies that they are experiencing an aura; and the subject administers the seletracetam. In some embodiments, the subject identifies that they are experiencing a prodrome; and the subject administers the seletracetam. In some embodiments, the subject identifies that they are experiencing an acute seizure, a seizure with aura or prodrome, a reflex seizure, a catamenial seizure, a focal onset seizure with retained awareness, a secondarily generalized seizure with focal onset, an absence seizure, a myoclonic seizure, a tonic seizure, an atonic seizure, a clonic seizure, a tonic-clonic seizure, an epileptic spasm, a focal seizure with or without altered awareness, a focal onset seizure without retained awareness, a status epilepticus, a subclinical seizure, or an electrographic seizure; and the subject administers the seletracetam. In preferred embodiments, the subject identifies that they are experiencing a focal onset seizure with retained awareness, a reflex seizure, or a seizure with aura or prodrome; and the subject administers the seletracetam. In more preferred embodiments, the subject identifies that they are experiencing a focal onset seizure with retained awareness; and the subject administers the seletracetam. In some embodiments, the subject administers the seletracetam within 15 minutes, 10 minutes, 7 minutes, 5 minutes, 3 minutes, 2 minutes, 1 minute, 30 seconds, or 20 seconds of the identification. In preferred embodiments, the subject administers the selectracetam within 5 minutes of the identification. In more preferred embodiments, the subject administers the seletracetam within 2 minutes of the identification.

In certain embodiments, the subject is sleep deprived, is experiencing stress, is experiencing hormone changes during their menstrual cycle, has taken a recreational drug, is experiencing drug withdrawal, is experiencing a febrile illness, or has missed or taken an incorrect dosage of their chronic antiseizure medication.

In some embodiments, the subject is sleep deprived. In certain embodiments, the subject is experiencing stress.

In some embodiments, the subject is experiencing hormone changes during their menstrual cycle. In certain embodiments, the subject is experiencing a drop in progesterone. In some embodiments, the subject is in the luteal phase, the menstrual phase, or the ovulatory phase of their menstrual cycle.

In certain embodiments, the subject has taken a recreational drug or is experiencing drug withdrawal. In some embodiments, the subject has taken a recreational drug in the last 72 hours, 48 hours, 24 hours, 12 hours, 6 hours, 3 hours, 2 hours, or 1 hour. In certain embodiments, the subject has taken alcohol, cocaine, amphetamine, methamphetamine, heroin, phencyclidine, cannabis, or MDMA. In some embodiments, the subject is experiencing withdrawal from alcohol, cocaine, amphetamine, methamphetamine, heroin, phencyclidine, cannabis, or MDMA.

In some embodiments, the subject is experiencing a febrile illness. In certain embodiments, the febrile illness is caused by a bacterial infection, a viral infection, a parasite infection, an autoimmune disorder, or a heat stroke.

In certain embodiments, the subject has missed or taken an incorrect dosage of their chronic antiseizure medication. In some embodiments, the subject has taken an incorrect dosage of their chronic antiseizure medication. In certain embodiments, the subject has missed at least one dose, at least two consecutive doses, or at least three consecutive doses of their chronic antiseizure medication.

In certain aspects, provided herein is a method of stabilizing the progression of a focal onset seizure with retained awareness in a subject in need thereof comprising administering seletracetam to the subject intranasally, buccally, or sublingually. Administration of seletracetam intranasally, buccally, or sublingually to a subject experiencing a focal onset seizure with retained awareness may stabilize the progression (e.g., halt, slow, or delay the progression) of the seizure to a focal onset seizure without awareness, or to a bilateral tonic-clonic seizure (which manifests as a convulsion).

In certain aspects, provided herein is a method of terminating a seizure in a subject in need thereof comprising administering seletracetam to the subject intranasally, buccally, or sublingually.

In certain aspects, provided is a method of administering seletracetam to a subject comprising administering seletracetam to the subject intranasally, buccally, or sublingually. In preferred embodiments, the seletracetam is administered intranasally. In some embodiments, the seletracetam is administered buccally or sublingually. In certain embodiments, the seletracetam is administered buccally. In some embodiments, the seletracetam is administered sublingually.

In certain embodiments, the seletracetam is administered intranasally at a dose of 1 mg to 300 mg, 1 mg to 250 mg, 1 mg to 200 mg, 1 mg to 150 mg, 1 mg to 125 mg, 1 mg to 100 mg, 1 mg to 80 mg, 1 mg to 60 mg, 1 mg to 50 mg, 1 mg to 40 mg, 1 mg to 25 mg, 1 mg to 15 mg, 1 mg to 10 mg, 1 mg to 5 mg, 5 mg to 300 mg, 5 mg to 250 mg, 5 mg to 200 mg, 5 mg to 150 mg, 5 mg to 125 mg, 5 mg to 100 mg, 5 mg to 80 mg, 5 mg to 60 mg, 5 mg to 50 mg, 5 mg to 40 mg, 5 mg to 25 mg, 5 mg to 15 mg, 5 mg to 10 mg, 10 mg to 300 mg, 10 mg to 250 mg, 10 mg to 200 mg, 10 mg to 150 mg, 10 mg to 125 mg, 10 mg to 100 mg, 10 mg to 80 mg, 10 mg to 60 mg, 10 mg to 50 mg, 10 mg to 40 mg, 10 mg to 25 mg, 10 mg to 15 mg, 15 mg to 300 mg, 15 mg to 250 mg, 15 mg to 200 mg, 15 mg to 150 mg, 15 mg to 125 mg, 15 mg to 100 mg, 15 mg to 80 mg, 15 mg to 60 mg, 15 mg to 50 mg, 15 mg to 40 mg, 15 mg to 25 mg, 25 mg to 300 mg, 25 mg to 250 mg, 25 mg to 200 mg, 25 mg to 150 mg, 25 mg to 125 mg, 25 mg to 100 mg, 25 mg to 80 mg, 25 mg to 60 mg, 25 mg to 50 mg, 25 mg to 40 mg, 40 mg to 300 mg, 40 mg to 250 mg, 40 mg to 200 mg, 40 mg to 150 mg, 40 mg to 125 mg, 40 mg to 100 mg, 40 mg to 80 mg, 40 mg to 60 mg, 40 mg to 50 mg, 50 mg to 300 mg, 50 mg to 250 mg, 50 mg to 200 mg, 50 mg to 150 mg, 50 mg to 125 mg, 50 mg to 100 mg, 50 mg to 80 mg, 50 mg to 60 mg, 60 mg to 300 mg, 60 mg to 250 mg, 60 mg to 200 mg, 60 mg to 150 mg, 60 mg to 125 mg, 60 mg to 100 mg, 60 mg to 80 mg, 80 mg to 300 mg, 80 mg to 250 mg, 80 mg to 200 mg, 80 mg to 150 mg, 80 mg to 125 mg, 80 mg to 100 mg, 100 mg to 300 mg, 100 mg to 250 mg, 100 mg to 200 mg, 100 mg to 150 mg, 100 mg to 125 mg, 125 mg to 300 mg, 125 mg to 250 mg, 125 mg to 200 mg, 125 mg to 150 mg, 150 mg to 300 mg, 150 mg to 250 mg, 150 mg to 200 mg, 200 mg to 300 mg, 200 mg to 250 mg, or 250 mg to 300 mg. In some embodiments, the seletracetam is administered intranasally at a dose of about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 70 mg, about 80 mg, about 90

mg, about 100 mg, about 125 mg, about 150 mg, about 200 mg, about 250 mg, or about 300 mg. In preferred embodiments, the seletracetam is administered intranasally at a dose of 10 mg to 80 mg. In more preferred embodiments, the seletracetam is administered intranasally at a dose of about 10 mg, about 20 mg, about 30 mg, about 40 mg, or about 50 mg.

In certain embodiments, the seletracetam is administered buccally at a dose of 1 mg to 300 mg, 1 mg to 250 mg, 1 mg to 200 mg, 1 mg to 150 mg, 1 mg to 125 mg, 1 mg to 100 mg, 1 mg to 80 mg, 1 mg to 60 mg, 1 mg to 50 mg, 1 mg to 40 mg, 1 mg to 25 mg, 1 mg to 15 mg, 1 mg to 10 mg, 1 mg to 5 mg, 5 mg to 300 mg, 5 mg to 250 mg, 5 mg to 200 mg, 5 mg to 150 mg, 5 mg to 125 mg, 5 mg to 100 mg, 5 mg to 80 mg, 5 mg to 60 mg, 5 mg to 50 mg, 5 mg to 40 mg, 5 mg to 25 mg, 5 mg to 15 mg, 5 mg to 10 mg, 10 mg to 300 mg, 10 mg to 250 mg, 10 mg to 200 mg, 10 mg to 150 mg, 10 mg to 125 mg, 10 mg to 100 mg, 10 mg to 80 mg, 10 mg to 60 mg, 10 mg to 50 mg, 10 mg to 40 mg, 10 mg to 25 mg, 10 mg to 15 mg, 15 mg to 300 mg, 15 mg to 250 mg, 15 mg to 200 mg, 15 mg to 150 mg, 15 mg to 125 mg, 15 mg to 100 mg, 15 mg to 80 mg, 15 mg to 60 mg, 15 mg to 50 mg, 15 mg to 40 mg, 15 mg to 25 mg, 25 mg to 300 mg, 25 mg to 250 mg, 25 mg to 200 mg, 25 mg to 150 mg, 25 mg to 125 mg, 25 mg to 100 mg, 25 mg to 80 mg, 25 mg to 60 mg, 25 mg to 50 mg, 25 mg to 40 mg, 40 mg to 300 mg, 40 mg to 250 mg, 40 mg to 200 mg, 40 mg to 150 mg, 40 mg to 125 mg, 40 mg to 100 mg, 40 mg to 80 mg, 40 mg to 60 mg, 40 mg to 50 mg, 50 mg to 300 mg, 50 mg to 250 mg, 50 mg to 200 mg, 50 mg to 150 mg, 50 mg to 125 mg, 50 mg to 100 mg, 50 mg to 80 mg, 50 mg to 60 mg, 60 mg to 300 mg, 60 mg to 250 mg, 60 mg to 200 mg, 60 mg to 150 mg, 60 mg to 125 mg, 60 mg to 100 mg, 60 mg to 80 mg, 80 mg to 300 mg, 80 mg to 250 mg, 80 mg to 200 mg, 80 mg to 150 mg, 80 mg to 125 mg, 80 mg to 100 mg, 100 mg to 300 mg, 100 mg to 250 mg, 100 mg to 200 mg, 100 mg to 150 mg, 100 mg to 125 mg, 125 mg to 300 mg, 125 mg to 250 mg, 125 mg to 200 mg, 125 mg to 150 mg, 150 mg to 300 mg, 150 mg to 250 mg, 150 mg to 200 mg, 200 mg to 300 mg, 200 mg to 250 mg, or 250 mg to 300 mg. In some embodiments, the seletracetam is administered buccally at a dose of about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 125 mg, about 150 mg, about 200 mg, about 250 mg, or about 300 mg. In preferred embodiments, the seletracetam is administered buccally at a dose of 10 mg to 80 mg. In more preferred embodiments, the seletracetam is administered bucally at a dose of about 10 mg, about 20 mg, about 30 mg, about 40 mg, or about 50 mg.

In certain embodiments, the seletracetam is administered sublingually at a dose of 1 mg to 300 mg, 1 mg to 250 mg, 1 mg to 200 mg, 1 mg to 150 mg, 1 mg to 125 mg, 1 mg to 100 mg, 1 mg to 80 mg, 1 mg to 60 mg, 1 mg to 50 mg, 1 mg to 40 mg, 1 mg to 25 mg, 1 mg to 15 mg, 1 mg to 10 mg, 1 mg to 5 mg, 5 mg to 300 mg, 5 mg to 250 mg, 5 mg to 200 mg, 5 mg to 150 mg, 5 mg to 125 mg, 5 mg to 100 mg, 5 mg to 80 mg, 5 mg to 60 mg, 5 mg to 50 mg, 5 mg to 40 mg, 5 mg to 25 mg, 5 mg to 15 mg, 5 mg to 10 mg, 10 mg to 300 mg, 10 mg to 250 mg, 10 mg to 200 mg, 10 mg to 150 mg, 10 mg to 125 mg, 10 mg to 100 mg, 10 mg to 80 mg, 10 mg to 60 mg, 10 mg to 50 mg, 10 mg to 40 mg, 10 mg to 25 mg, 10 mg to 15 mg, 15 mg to 300 mg, 15 mg to 250 mg, 15 mg to 200 mg, 15 mg to 150 mg, 15 mg to 125 mg, 15 mg to 100 mg, 15 mg to 80 mg, 15 mg to 60 mg, 15 mg to 50 mg, 15 mg to 40 mg, 15 mg to 25 mg, 25 mg to 300 mg, 25 mg to 250 mg, 25 mg to 200 mg, 25 mg to 150 mg, 25 mg to 125 mg, 25 mg to 100 mg, 25 mg to 80 mg, 25 mg to 60 mg, 25 mg to 50 mg, 25 mg to 40 mg, 40 mg to 300 mg, 40 mg to 250 mg, 40 mg to 200 mg, 40 mg to 150 mg, 40 mg to 125 mg, 40 mg to 100 mg, 40 mg to 80 mg, 40 mg to 60 mg, 40 mg to 50 mg, 50 mg to 300 mg, 50 mg to 250 mg, 50 mg to 200 mg, 50 mg to 150 mg, 50 mg to 125 mg, 50 mg to 100 mg, 50 mg to 80 mg, 50 mg to 60 mg, 60 mg to 300 mg, 60 mg to 250 mg, 60 mg to 200 mg, 60 mg to 150 mg, 60 mg to 125 mg, 60 mg to 100 mg, 60 mg to 80 mg, 80 mg to 300 mg, 80 mg to 250 mg, 80 mg to 200 mg, 80 mg to 150 mg, 80 mg to 125 mg, 80 mg to 100 mg, 100 mg to 300 mg, 100 mg to 250 mg, 100 mg to 200 mg, 100 mg to 150 mg, 100 mg to 125 mg, 125 mg to 300 mg, 125 mg to 250 mg, 125 mg to 200 mg, 125 mg to 150 mg, 150 mg to 300 mg, 150 mg to 250 mg, 150 mg to 200 mg, 200 mg to 300 mg, 200 mg to 250 mg, or 250 mg to 300 mg. In some embodiments, the seletracetam is administered sublingually at a dose of about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 125 mg, about 150 mg, about 200 mg, about 250 mg, or about 300 mg. In preferred embodiments, the seletracetam is administered sublingually at a dose of 10 mg to 80 mg. In more preferred embodiments, the seletracetam is administered sublingually at a dose of about 10 mg, about 20 mg, about 30 mg, about 40 mg, or about 50 mg.

In some aspects, provided is a method of treating a pain in a subject in need thereof comprising administering seletracetam to the subject intranasally, buccally, or sublingually. In some embodiments, the pain comprises neuropathic pain, peripheral nerve pain, migraine,

visceral pain, cancer break through pain, post-surgical pain, chronic pain, neuralgia, or cluster headache.

In certain aspects, provided is a method of treating a neurological or psychiatric disorder in a subject in need thereof comprising administering seletracetam to the subject intranasally, buccally, or sublingually. In some embodiments, the neurological or psychiatric disorder comprises bipolar disorder, mania, depression, anxiety, cerebral ischemia, essential tremor, neonatal cerebral hemorrhage, amyotrophic lateral sclerosis, spasticity, Parkinson's disease, dementia, Alzheimer's disease, Mild Cognitive Impairment (MCI), Age-related Cognitive Decline (ARCD), or Age-Associated Memory Impairment (AAMI). Related treatment methods comprising administration of seletracetam are described, for example, in US Patent Application Publication No. 2024/0293363 A1, which is incorporated by reference herein.

In certain embodiments, the seletracetam is administered buccally or sublingually. In some embodiments, the seletracetam is administered buccally. In certain embodiments, the seletracetam is administered sublingually.

In some embodiments, the method provides therapeutic plasma levels of seletracetam within 45 minutes (e.g., within 30 minutes) of the administering. In certain embodiments, the method provides at least 25 ng/ml (e.g., at least 50 ng/ml) seletracetam in the subject's plasma within 30 minutes of the administering. In certain embodiments, the method provides at least 50 ng/ml seletracetam in the subject's plasma within 15 minutes of the administering. In some embodiments, the method provides at least 50 ng/ml seletracetam in the subject's plasma within 5 minutes of the administering. In certain embodiments, the method provides at least 100 ng/ml seletracetam in the subject's plasma within 5 minutes of the administering. In certain embodiments, the method provides at least 100 ng/ml seletracetam in the subject's plasma within 15 minutes of the administering. In some embodiments, the method provides a first-pass effect of less than 40% compared to oral administration.

In certain aspects, provided is a pharmaceutical formulation comprising seletracetam and a pharmaceutically acceptable liquid carrier. In some embodiments, the formulation is a solution, a suspension, or an emulsion. In certain embodiments, the formulation is a solution. In some embodiments, the liquid carrier is water.

In certain embodiments, the formulation further comprises a buffering agent. In some embodiments, the buffering agent comprises hydrochloric acid, acetic acid, citric acid, sodium

hydroxide, sodium citrate, sodium carbonate, sodium tetraborate, sodium phosphate, sodium acetate, sodium bicarbonate, potassium hydrogen phosphate, or potassium phosphate.

In certain embodiments, the formulation further comprises a preservative. In some embodiments, the preservative comprises sodium bisulfite, edetate disodium, sodium bisulfate, sodium thiosulfate, benzalkonium chloride, benzethonium chloride, chlorobutanol, thimerosal, phenylmercuric acetate, benzyl alcohol, phenylcarbinol, phenylmercuric nitrate, methylparaben, propylparaben, polyvinyl alcohol, phenylethyl alcohol, sodium benzoate, benzoic acid, phenyl ethyl alcohol, or ethylenediaminetetraacetic acid (EDTA). In certain embodiments, the concentration of the preservative in the formulation is about 0.01% to about 0.50% (w/w).

In certain embodiments, the formulation further comprises a flavoring agent, a sweetener, an odorant, or a taste-masking agent. In some embodiments, the formulation comprises a flavoring agent, wherein the flavoring agent comprises vanilla extract, cinnamon, ginger, vanillin, linalool, coumarin, or a citrus oil. In certain embodiments, the formulation comprises a sweetener, wherein the sweetener comprises sucrose, xylitol, sodium saccharin, cyclamate, high fructose corn syrup, aspartame, acesulfame K, thaumatin, or stevia. In some embodiments, the formulation comprises a taste-masking agent, wherein the taste-masking agent comprises sodium chloride, citric acid, or sodium bicarbonate.

In certain embodiments, the formulation further comprises a mucoadhesive agent or a thickening agent. In some embodiments, the formulation comprises a mucoadhesive agent, wherein the mucoadhesive agent comprises hydroxyethyl cellulose (e.g., Natrosol™ 250 M), hydroxypropyl cellulose, dodecyl maltoside, sucrose dodecanoate, fish gelatin, gelatin type A, hyaluronic acid, or mannitol. In some embodiments, the mucoadhesive agent comprises hydroxyethyl cellulose. In certain embodiments, the formulation comprises a thickening agent, wherein the thickening agent comprises methylcellulose, ethyl cellulose, microchrystalline cellulose, hydroxypropyl methylcellulose, hydroxyethylcellulose, (e.g., Natrosol™ 250 M), sodium carboxymethylcellulose, polyvinyl pyrrolidone, polyvinyl alcohol, sodium chondroitin sulfate, sodium hyaluronate, chitosan, tetradecylmaltoside, hydroxypropylcellulose, or hyaluronic acid. In certain embodiments, the hyaluronic acid is a hyaluronic acid polymer having a molecular weight of about 3,000 Dalton, about 10,000 Dalton, about 25,000 Dalton, about 50,000 Dalton, about 100,000 Dalton, about 350,000 Dalton, about 1,000,000 Dalton, or

about 3,000,000 Dalton. In some embodiments, the concentration of the mucoadhesive agent or the thickening agent is 0.05% to 3.0% (w/w).

In certain embodiments, the formulation further comprises an antioxidant. In some embodiments, the antioxidant comprises ascorbic acid, sodium bisulfite, butylated hydroxytoluene, sodium metabisulfite, or tocopherol.

In certain embodiments, the formulation further comprises a humectant. In some embodiments, the humectant comprises glycerin, sorbitol, dexpanthenol, or mannitol.

In certain embodiments, the formulation further comprises a surfactant. In some embodiments, the surfactant comprises dodecyl maltoside, tetradecyl maltoside, sucrose dodecanoate, sucrose mono-stearate, sucrose di-stearate, polysorbate, polysorbate 80, polysorbate 20, a polyethylene glycol ester, a polyethylene glycol, a glycerol ether, a glyceryl monoleate, lecithin, polysorbate 80 NF, polyoxyethylene 20 sorbitan monolaurate, polyoxyethylene (4) sorbitan monolaurate, polyoxyethylene 20 sorbitan monopalmitate, polyoxyethylene 20 sorbitan monostearate, polyoxyethylene (4) sorbitan monostearate, polyoxyethylene 20 sorbitan tristearate, polyoxyethylene (5) sorbitan monooleate, polyoxyethylene 20 sorbitan trioleate, 20 polyoxyethylene 20 sorbitan monoisostearate, sorbitan monooleate, sorbitan monolaurate, sorbitan monopalmitate, sorbitan monostearate, sorbitan trilaurate, sorbitan trioleate, or sorbitan tristearate.

In certain embodiments, the formulation further comprises a penetration enhancer. In certain embodiments, the penetration enhancer comprises dodecyl maltoside, tetradecyl maltoside, a bile salt such as taurodeoxycholate, sodium dodecyl sulfate (SDS), dimethyl sulfoxide (DMSO), N-lauroyl sacrcosine, sorbitan monolaurate, stearyl methacrylate, N-dodecylazacyclohcptan-2-one, N-dodecyl-2-pyrrolidinone, N-dodecyl-2-piperidinone, 2-(1-nonyl)-1,3-dioxolane, N-(2-methoxymethyl) dodecylamine, N-dodecylethanolamine, N-dodecyl-N-(2-methoxymethyl)acetamide, 1-N-dodecyl-2-pyrrolidone-5-carboxylic acid, 2-pentyl-2-oxo-pyrrolidineacetic acid, 2-dodecyl-2-oxo-1-pyrrolidineacetic acid, 2-dodecyl-2-oxo-l-pyrrolidineacetic acid, 1-azacylioheptan-2-one-dodecylacetic acid, menthol, propylene glycol, glycerol monostearate, sorbitol monolaurate, glycerol dilaurate, tocopherol acetate, phosphatidyl choline, glycerol, polyethyleneglycol, a monoglyceride, a diglyceride, a triglyceride, lecithin, or sodium lauryl sulfate.

In certain embodiments, the formulation does not comprise a benzodiazepine.

In some aspects, provided is a nasal spray device comprising seletracetam.

In certain aspects, provided is an oromucosal spray device comprising seletracetam.

In some embodiments, the device comprises the formulation according to embodiments described herein. In certain embodiments, the device is a unit-dose device. In some embodiments, the device is a bi-dose device or a multi-dose device. In certain embodiments, the device comprises a mechanical spray pump. In some embodiments, the device is configured to dispense 25 µL to 200 µL of the formulation described herein per spray actuation. In certain embodiments, the device is configured to dispense about 50 µL, about 75 µL, about 100 µL, about 160 µL, or about 200 µL of the formulation described herein per spray actuation. In certain embodiments, the device is configured to dispense about 50 µL of the formulation described herein per actuation of the device. In some embodiments, the device is configured to dispense about 100 µL of the formulation described herein per actuation of the device. In some embodiments, the device is configured to dispense about 160 µL of the formulation described herein per actuation of the device.

In some embodiments, the mechanical spray pump comprises a metered dose spray pump configured to dispense a dose of 25 µL to 200 µL per spray actuation. In certain embodiments, the device is configured to dispense a dose of about 50 µL, about 75 µL about 100 µL, about 160 µL, or about 200 µL per spray actuation.

In some aspects, provided is an orally disintegrating tablet comprising seletracetam.

In some embodiments, the seletracetam has a particle size of 20 nanometers to 10 micrometers.

In certain embodiments, the tablet further comprises an alkyl saccharide. In some embodiments, the alkyl saccharide is sucrose mono-stearate, sucrose di-stearate, tetradecyl maltoside, dodecyl maltoside, tetradecylm altoside, or sucrose dodecanoate. In certain embodiments, the concentration of the alkyl saccharide is 0.1 wt.% to 10 wt.%.

In certain embodiments, the tablet further comprises hydroxyethyl cellulose (e.g., Natrosol™ 250 M), hydroxypropyl cellulose, fish gelatin, gelatin type A, mannitol, or hyaluronic acid. In certain embodiments, the hyaluronic acid is a hyaluronic acid polymer having a molecular weight of about 3,000 Dalton, about 10,000 Dalton, about 25,000 Dalton, about 50,000 Dalton, about 100,000 Dalton, about 350,000 Dalton, about 1,000,000 Dalton, or about 3,000,000 Dalton.

In some embodiments, the tablet further comprises a coloring agent. In certain embodiments, the coloring agent comprises a titanium oxide or an iron oxide.

In certain embodiments, the tablet further comprises a preservative. In some embodiments, the preservative comprises sodium bisulfite, edetate disodium, sodium bisulfate, sodium thiosulfate, benzalkonium chloride, benzethonium chloride, chlorobutanol, thimerosal, phenylmercuric acetate, benzyl alcohol, phenylcarbinol, phenylmercuric nitrate, methylparaben, propylparaben, polyvinyl alcohol, phenylethyl alcohol, sodium benzoate, benzoic acid, phenyl ethyl alcohol, or ethylenediaminetetraacetic acid (EDTA).

In certain embodiments, the tablet further comprises a flavoring agent, a sweetener, an odorant, or a taste-masking agent. In some embodiments, the tablet comprises a flavoring agent, wherein the flavoring agent comprises vanilla extract, cinnamon, ginger, vanillin, linalool, coumarin, or a citrus oil. In certain embodiments, the tablet comprises a sweetener, wherein the sweetener comprises sucrose, xylitol, sodium saccharin, cyclamate, high fructose corn syrup, aspartame, acesulfame K, thaumatin, or stevia. In some embodiments, the tablet comprises a taste-masking agent, wherein the taste-masking agent comprises sodium chloride, citric acid, or sodium bicarbonate.

In certain embodiments, the tablet further comprises a mucoadhesive agent. In some embodiments, the mucoadhesive agent comprises hydroxyethyl cellulose (e.g., Natrosol^{TM} 250 M), hydroxypropyl cellulose, dodecyl maltoside, sucrose dodecanoate, fish gelatin, gelatin type A, hyaluronic acid, or mannitol. In certain embodiments, the hyaluronic acid is ahyaluronic acid polymer having a molecular weight of about 3,000 Dalton, or about 10,000 Dalton, or about 25,000 Dalton, or about 50,000 Dalton, or about 100,000 Dalton, or about 350,000 Dalton, or about 1,000,000 Dalton, or about 3,000,000 Dalton. In preferred embodiments, the mucoadhesive agent comprises hydroxyethyl cellulose. In certain embodiments, the concentration of the mucoadhesive agent is 0.05% to 3.0% (w/w).

In certain embodiments, the tablet further comprises an antioxidant. In some embodiments, the antioxidant comprises ascorbic acid, sodium bisulfite, butylated hydroxytoluene, sodium metabisulfite, or tocopherol.

In certain embodiments, the tablet further comprises a penetration enhancer. In some embodiments, the penetration enhancer comprises dodecyl maltoside, tetradecyl maltoside, a bile salt(e.g., taurodeoxycholate), sodium dodecyl sulfate (SDS), dimethyl sulfoxide (DMSO), N-

lauroyl sacrcosine, sorbitan monolaurate, stearyl methacrylate, N-dodecylazacyclohcptan-2-one, N-dodecyl-2-pyrrolidinone, N-dodecyl-2-piperidinone, 2-(1-nonyl)-1,3-dioxolane, N-(2-methoxymethyl) dodecylamine, N-dodecylethanolamine, N-dodecyl-N-(2-methoxymethyl)acetamide, 1-N-dodecyl-2-pyrrolidone-5-carboxylic acid, 2-pentyl-2-oxo-pyrrolidineacetic acid, 2-dodecyl-2-oxo-1-pyrrolidineacetic acid, 2-dodecyl-2-oxo-l-pyrrolidineacetic acid, 1-azacylioheptan-2-one-dodecylacetic acid, menthol, propylene glycol, glycerol monostearate, sorbitol monolaurate, glycerol dilaurate, tocopherol acetate, phosphatidyl choline, glycerol, polyethyleneglycol, a monoglyceride, a diglyceride, a triglyceride, lecithin, or sodium lauryl sulfate.

In certain embodiments, the tablet does not comprise a benzodiazepine.

In some aspects, provided is a mucoadhesive film comprising seletracetam.

In certain embodiments, the film further comprises a polymer comprising methyl cellulose, hydroxypropyl cellulose, carboxymethylcellulose, cellulose acetate, ethylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, an alginate, a gelatin, pullulan, pectin, locust bean gum, xanthan gum, sodium alginate, gum Arabic, nitrocellulose, a poly(ethylene oxide), a polyoxypropylene, or a polyvinylpyrrolidone. In some embodiments, the polymer comprises ethylcellulose, poly(ethylene oxide), hydroxypropyl cellulose, or hyaluronic acid. In certain embodiments, the hyaluronic acid is a hyaluronic acid polymer having a molecular weight of about 3,000 Dalton, about 10,000 Dalton, about 25,000 Dalton, about 50,000 Dalton, about 100,000 Dalton, about 350,000 Dalton, about 1,000,000 Dalton, or about 3,000,000 Dalton.

In some embodiments, the film further comprises a coloring agent. In certain embodiments, the coloring agent comprises a titanium oxide or an iron oxide.

In some embodiments, the film is a monolayer film. In certain embodiments, the film is a bilayer film. In some embodiments, the film comprises at least three layers. In certain embodiments, the film comprises a first layer comprising seletracetam and a second layer comprising a base. In some embodiments, the base comprises a polyamine, calcium hydroxide, magnesium hydroxide, potassium hydroxide, sodium hydroxide, calcium carbonate, iron carbonate, magnesium carbonate, zinc carbonate, sodium acetate, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, sodium phosphate monobasic, sodium phosphate dibasic, sodium phosphate tribasic, potassium phosphate monobasic, potassium

phosphate dibasic, or potassium phosphate tribasic. In certain embodiments, the base comprises a polyamine, wherein the polyamine comprises dimethylaminoethyl-acrylate, dimethylaminoethyl-methacrylate, dimethylaminopropyl-acrylate, dimethylaminpropyl-methacrylate, chitosan, polyethyleimine, polylysine, polyvinylimidazole, or polyvinylamine.

In some embodiments, the film further comprises a preservative. In certain embodiments, the preservative comprises sodium bisulfite, edetate disodium, sodium bisulfate, sodium thiosulfate, benzalkonium chloride, benzethonium chloride, chlorobutanol, thimerosal, phenylmercuric acetate, benzyl alcohol, phenylcarbinol, phenylmercuric nitrate, methylparaben, propylparaben, polyvinyl alcohol, phenylethyl alcohol, sodium benzoate, benzoic acid, phenyl ethyl alcohol, or ethylenediaminetetraacetic acid (EDTA).

In some embodiments, the film further comprises a flavoring agent, a sweetener, an odorant, or a taste-masking agent. In certain embodiments, the film comprises a flavoring agent, wherein the flavoring agent comprises vanilla extract, cinnamon, ginger, vanillin, linalool, coumarin, or a citrus oil. In some embodiments, the film comprises a sweetener, wherein the sweetener comprises sucrose, xylitol, sodium saccharin, cyclamate, high fructose corn syrup, aspartame, acesulfame K, thaumatin, or stevia. In certain embodiments, the film comprises a taste-masking agent, wherein the taste-masking agent comprises sodium chloride, citric acid, or sodium bicarbonate.

In some embodiments, the film further comprises a mucoadhesive agent. In certain embodiments, the mucoadhesive agent comprises hydroxyethyl cellulose, hydroxypropyl cellulose, dodecyl maltoside, sucrose dodecanoate, fish gelatin, gelatin type A, hyaluronic acid, or mannitol. In certain embodiments, the hyaluronic acid is a hyaluronic acid polymer having a molecular weight of about 3,000 Dalton, about 10,000 Dalton, about 25,000 Dalton, about 50,000 Dalton, about 100,000 Dalton, about 350,000 Dalton, about 1,000,000 Dalton, or about 3,000,000 Dalton. In certain embodiments, the mucoadhesive agent comprises hydroxyethyl cellulose. In some embodiments, the concentration of the mucoadhesive agent is 0.05% to 3.0% (w/w).

In certain embodiments, the film further comprises an antioxidant. In some embodiments, the antioxidant comprises ascorbic acid, sodium bisulfite, butylated hydroxytoluene, sodium metabisulfite, or tocopherol.

In some embodiments, the film further comprises a penetration enhancer. In certain embodiments, the penetration enhancer comprises dodecyl maltoside, tetradecyl maltoside, a bile salt, sodium dodecyl sulfate (SDS), dimethyl sulfoxide (DMSO), N-lauroyl sacrcosine, sorbitan monolaurate, stearyl methacrylate, N-dodecylazacyclohcptan-2-one, N-dodecyl-2-pyrrolidinone, N-dodecyl-2-piperidinone, 2-(1-nonyl)-1,3-dioxolane, N-(2-methoxymethyl) dodecylamine, N-dodecylethanolamine, N-dodecyl-N-(2-methoxymethyl)acetamide, 1-N-dodecyl-2-pyrrolidone-5-carboxylic acid, 2-pentyl-2-oxo-pyrrolidineacetic acid, 2-dodecyl-2-oxo-1-pyrrolidineacetic acid, 2-dodecyl-2-oxo-l-pyrrolidineacetic acid, 1-azacylioheptan-2-one-dodecylacetic acid, menthol, propylene glycol, glycerol monostearate, sorbitol monolaurate, glycerol dilaurate, tocopherol acetate, phosphatidyl choline, glycerol, polyethyleneglycol, a monoglyceride, a diglyceride, a triglyceride, lecithin, or sodium lauryl sulfate.

In some embodiments, the film does not comprise a benzodiazepine.

Sublingual, intranasal, or buccal administration of seletracetam may be considered for acute as well as chronic treatment of patients with epilepsy who are unable to take oral medication. In some patients, epilepsy is associated with profound brain dysfunction, either early life maldevelopment or regression due to genetic or other causes, or secondary to uncontrolled epilepsy, so-called developmental epileptic encephalopathy (DEE), or because of severe injury to the brain later in life caused for instance by head injury or stroke. Such patients may not be able to take oral medications on command or swallow them. This may limit the ability to treat epilepsy in these patients. For these patients, a non-oral, non-IV route of administration of chronic antiseizure medication would be an advantage. Non-oral non-IV routes of administration may include sublingual, intranasal, or buccal administration routes. As with the treatment of ARS or REST treatment, the only class of medication available for such treatment at present are the benzodiazepines. The availability of sublingually or intranasally formulated non-benzodiazepine antiseizure medication such as seletracetam would offer a significant advantage for both, acute seizure rescue treatment, and for chronic epilepsy treatment of such patients.

Also, selectracetam represents a unique treatment option for patients with epilepsy syndromes which are caused by $GABA_A$ receptor mutations or which cannot be treated with benzodiazepines due to the $GABA_A$ receptor mutation. As these syndromes are severe and occur in childhood, the sublingual, buccal or intranasal administration route adds the advantage that the

medication must not be swallowed, and thus can be administered in these patients even if they are not able or willing to swallow tablets.

The oral administration of seletracetam (including as an organic–inorganic ionic co-crystal with inorganic crystal-forming agents like e.g. calcium, lithium or magnesium), has been described in the literature [Bennett, B., Matagne, A., et al. (2007), Neurotherapeutics, 4(1), 117-122; Braga, D., et al. (2018), CrystEngComm, 20(16), 2212-2220; Wouters, J. et al, (2013), CrystEngComm, 15(44), 8898-8902].

Following oral administration of seletracetam, therapeutic plasma levels are reached within about 1 h after dosing in fasted subjects. However, if administered in non-fasted subjects, the absorption is largely delayed by up to 4 h and the maximal plasma level reached is reduced by 39% [Bennett et al, 2007, Neurotherapeutics, 4(1), 117-122]. Seletracetam is extensively metabolized following oral administration. 78% of the seletracetam dose administered orally is excreted as acid metabolite, indicating that less than 25% of the parent drug is excreted unchanged. Seletracetam undergoes substantial hepatic oxidative metabolism, including (but not limited to) first-pass metabolism. In contrast, following intravenous administration, therapeutic plasma levels are reached immediately, and hepatic first-pass metabolism is avoided, resulting in higher overall exposure. However, intravenous administration is generally not practicable for patients in need of rescue therapy outside of the hospital and may be difficult in any setting in some patients with poor venous access. Therefore, alternative routes of administration are needed, especially for treatment of patients with acute repetitive seizures who require a rapid onset of the pharmacological action of seletracetam, such as for rescue treatment. First-pass metabolism can be avoided if the drug is administered intranasally, or by buccal/sublingual administration. For both administration routes, food interaction is not of concern, and absorption starts immediately after administration, resulting in rapid absorption and achievement of therapeutic plasma levels. Following buccal/sublingual administration, therapeutic plasma levels may be achieved in less than 15-30 min after administration of an effective dose, while following intranasal administration, therapeutic plasma levels may be achieved within less than 5-15 min after administration of an effective dose.

In summary, there is a clear, as-yet unmet therapeutic need for new non-oral and non-IV formulations of seletracetam, which allow rapid absorption and reach of therapeutic plasma levels, for the intervention treatment in patients suffering from epilepsy or pain. Both intranasal

and buccal/sublingual formulations may be used to reach these goals, as these routes are usable even in cognitively disabled (e.g., intellectually disabled) or impaired patients and can be instantly used without any preparation either by the patient itself or by care givers to patients. These administration forms require minimal medical intervention, as they require only either spraying a nasal spray in one or both nostrils or placing a buccal / sublingual dosage form into the mouth either under the tongue or in the cheeks or in the space between the teeth and the lips, to allow for oromucosal absorption. The cognitive enhancing activity of seletracetam is further of advantage for all patients and especially for patients with an intellectual disability.

Sublingual Formulations

In certain aspects, the present disclosure provides formulations comprising seletracetam. In some embodiments, a method of treating or preventing epilepsy, epileptic seizures, acute repetitive seizures and other epilepsy-related symptoms including (but not limited to) CNS depression, cognitive impairment, impaired consciousness following or preceding seizures, or seizure-associated pain comprises administering the formulation to a subject in need thereof. In some embodiments, a method of treating or preventing pain (e.g. neuropathic pain, peripheral nerve pain, chronic pain, neuralgia, or migraine) comprises administering the formulation to a subject in need thereof. In certain embodiments, a method of treating or preventing bipolar disorders, mania, depression, anxiety, cerebral ischemia, essential tremor, neonatal cerebral hemorrhage, amyotrophic lateral sclerosis, spasticity, cognitive impairment or dementia including Alzheimer's disease, Mild Cognitive Impairment (MCI), Age-related Cognitive Decline (ARCD), Age-Associated Memory Impairment (AAMI) or Parkinson's disease comprises administering the formulation to a subject in need thereof. Related treatment methods comprising administration of seletracetam are described, for example, in US Patent Application Publication No. 2024/0293363 A1, which is incorporated by reference herein.

In some embodiments, a pharmaceutical composition in unit dosage form (e.g., a lozenge, a pill, a tablet, a film, or a strip) is formulated for sublingual or buccal administration, the unit dosage form having a first portion comprising seletracetam (e.g., a seletracetam co-crystal) and a second portion comprising a pH neutralizing and filling agent (e.g., polyamines, calcium hydroxide, magnesium hydroxide, potassium hydroxide, sodium hydroxide, calcium carbonate, iron carbonate, magnesium carbonate, zinc carbonate, sodium acetate, sodium carbonate,

potassium carbonate, sodium bicarbonate, potassium bicarbonate, sodium phosphate monobasic, sodium phosphate dibasic, sodium phosphate tribasic, potassium phosphate monobasic, potassium phosphate dibasic, potassium phosphate tribasic, mixtures thereof, or any other suitable base).

In certain embodiments, the unit dosage form is a film or a strip wherein the unit dosage form includes a mucoadhesive polymer. The mucoadhesive polymer can be, without limitation, any mucoadhesive polymer described herein, including methyl cellulose, hydroxy propyl cellulose, carboxymethylcellulose, alginates, hyaluronic acid and hyaluronic acid polymers including but not limited to hyaluronic acid polymer with a molecular weight of about 3,000 Dalton, or about 10,000 Dalton, or about 25,000 Dalton, or about 50,000 Dalton, or about 100,000 Dalton, or about 350,000 Dalton, or about 1,000,000 Dalton, or about 3,000,000 Dalton, or gelatine. In some embodiments, the pharmaceutical composition is a film or a strip, wherein the first portion is a first layer and the second portion is a second layer, the first layer being the drug-containing layer, and the second layer includes the pH-neutralizing agent and/or the mucoadhesive agent.

In certain embodiments, the sublingual or buccal or intranasal formulation includes an antioxidant. The antioxidant can be, without limitation, any antioxidant described herein, including ascorbic acid, sodium bisulfite, butylated hydroxytoluene, sodium metabisulfite, and tocopherol.

In some embodiments, the sublingual or buccal formulation includes a first portion that is a film including seletracetam (e.g., a seletracetam co-crystal) as micronized crystalline material, imbedded in a film-forming material, and it includes a second portion that is a particulate base on or within the unit dosage form. The particulate base can include, for example, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, sodium phosphate monobasic, sodium phosphate dibasic, sodium phosphate tribasic, potassium phosphate monobasic, potassium phosphate dibasic, potassium phosphate tribasic, or a mixture thereof.

In certain embodiments, the first portion of the unit dosage form is separated from the second portion of the unit dosage form by a barrier (e.g., a film separating and first drug-containing layer from a basic carrier layer in a multi-layered film, or a coating on a particulate base or seletracetam particle contained within the unit dosage form). The barrier can be neutral in

pH (e.g., between 6 and 7.8), separating the first portion from the basic second portion of the unit dosage form.

In a related aspect, a pharmaceutical composition formulated for sublingual or buccal administration comprises seletracetam particles (e.g., particles of a seletracetam co-crystal) having an effective particle size of from 20 nm to 20 μm. In some embodiments, the seletracetam crystals (e.g., seletracetam co-crystals) are not micronized prior to inclusion in the formulation, and thus are not size-controlled. Such is possible due to the good water solubility of seletracetam. In certain embodiments, the pharmaceutical composition is in a unit dosage form selected from a lozenge, a pill, a tablet, a film, or a strip. In other embodiments, the pharmaceutical composition is a sublingual or buccal gel. The sublingual or buccal formulations can include seletracetam (e.g., seletracetam co-crystal) particles having an effective particle size of from 1 μm to 20 μm (e.g., an effective particle size of from 1 μm to 15 μm, from 1 μm to 10 μm, from 1 μm to 8 μm, from 1 μm to 6 μm, from 1 μm to 5 μm, from 2 μm to 15 μm, from 3 μm to 15 μm, from 4 μm to 15 μm, from 2 μm to 10 μm, or from 2 μm to 6 μm).

In certain other embodiments, the sublingual or buccal formulation comprises seletracetam (e.g., seletracetam co-crystal) particles having an effective particle size of from 20 nm to 1 μm (e.g., an effective particle size of from 20 nm to 1 μm, from 40 nm to 1 μm, from 60 nm to 1 μm, from 80 nm to 1 μm, from 100 nm to 1 μm, from 20 nm to 800 nm, from 20 nm to 700 nm, from 50 nm to 700 nm, from 40 nm to 800 nm, from 60 nm to 800 nm, from 100 nm to 800 nm, from 60 nm to 700 nm, from 60 nm to 600 nm, from 100 nm to 600 nm, from 150 nm to 800 nm, or from 150 nm to 600 nm).

In still other embodiments, the sublingual or buccal formulation includes a mucoadhesive polymer. The mucoadhesive polymer can be, without limitation, any mucoadhesive polymer described herein.

In certain embodiments, the sublingual or buccal formulation in the unit dosage form is a film or a strip including a mucoadhesive polymer. The mucoadhesive polymer can be, without limitation, any mucoadhesive polymer described herein. For example, the film or strip can include a first layer and a second layer, the first layer comprising the seletracetam (e.g., seletracetam co-crystal) particles, and the second layer comprising a pH neutralizing/buffering agent (e.g., polyamines, calcium hydroxide, magnesium hydroxide, potassium hydroxide, sodium hydroxide, calcium carbonate, iron carbonate, magnesium carbonate, zinc carbonate,

sodium acetate, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, sodium phosphate monobasic, sodium phosphate dibasic, sodium phosphate tribasic, potassium phosphate monobasic, potassium phosphate dibasic, potassium phosphate tribasic, and mixtures thereof, or any other suitable base).

In still other embodiments, the sublingual or buccal formulation includes a surfactant, which may also serve as an absorption-enhancing agent. In certain embodiments, the surfactant comprises an alkyl glycoside (e.g. tetradecyl maltoside or dodecyl maltoside (Intravail®) as described by Rabinowicz et al, 2021 [Rabinowicz, A. L., Carrazana, E., & Maggio, E. T. (2021) Drugs in R&D, 21(4), 361-369]) or a saccharide alkyl ester. The surfactant may stabilize the biological activity and increase the bioavailability of the drug. The surfactant may be a suitable nontoxic, non-ionic alkyl glycoside having a hydrophobic alkyl joined by a linkage to a hydrophilic saccharide, as described in U.S. Patent No. 9,283,280, which is incorporated by reference. In certain embodiments, the surfactant comprises dodecyl maltoside, tetradecyl maltoside, sucrose dodecanoate, or sucrose mono- and di-stearate.

In a particular embodiment, the sublingual or buccal formulation in unit dosage form is a film or a strip comprising a surfactant. In some embodiments, the surfactant is an alkyl glycoside (e.g. tetradecyl maltoside or dodecyl maltoside (Intravail®)) or a saccharide alkyl ester. The film or strip may include a first layer and a second layer, the first layer being acidic and comprising the seletracetam (e.g. seletracetam co-crystal) particles and the second layer comprising a pH neutralizing agent (e.g., polyamines, calcium hydroxide, magnesium hydroxide, potassium hydroxide, sodium hydroxide, calcium carbonate, iron carbonate, magnesium carbonate, zinc carbonate, sodium acetate, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, sodium phosphate monobasic, sodium phosphate dibasic, sodium phosphate tribasic, potassium phosphate monobasic, potassium phosphate dibasic, potassium phosphate tribasic, mixtures thereof, or any other suitable base).

In certain embodiments, the sublingual or buccal formulation includes an antioxidant. In certain embodiments, the antioxidant comprises ascorbic acid, sodium bisulfite, butylated hydroxytoluene, sodium metabisulfite, or tocopherol.

In another aspect, a pharmaceutical composition formulated for sublingual administration comprises seletracetam complexed to an anionic polyelectrolyte (e.g., alginates, carrageenan, xanthan gum, polyacrylate, or carboxymethylcellulose). In certain embodiments, the sublingual

formulation includes an antioxidant. In some embodiments, the pharmaceutical composition is in a unit dosage form selected from a lozenge, a pill, a tablet, a film, or a strip. In certain embodiments, the pharmaceutical composition is a sublingual gel. In some embodiments, a pharmaceutical composition in unit dosage form formulated for sublingual administration comprises from 1 to 300 mg of seletracetam (e.g., from 1 to 15 mg, 10 to 50 mg, 12 to 30 mg, 20 to 50 mg, 15 to 30 mg, 35 to 50 mg, 35 to 75 mg, 50 to 100 mg, 75-150 mg 100 to 200 mg, or 200 to 300 mg of seletracetam). In some embodiments, the unit dosage form is a lozenge, a pill, a tablet, a film, or a strip including (but not limited to) seletracetam. In still other embodiments, the unit dosage form is a lozenge, a pill, a tablet, a film, or a strip including a solid solution of seletracetam. In certain embodiments, the pharmaceutical composition is in a unit dosage form including from 1 to 200 mg of seletracetam (e.g., from 1 to 5 mg, 4 to 10 mg, 6 to 15 mg, 8 to 20 mg, 10 to 25 mg, 12 to 30 mg, 20 to 35 mg, 25 to 50 mg, 30 to 50 mg, 30 to 75 mg, 50 to 100 mg, 75 to 150 mg, or 100 to 200 mg of seletracetam). In some embodiments, each unit dosage form can contain 3 ± 1 mg, 4 + 1 mg, 5 + 1 mg, 8 ± 2 mg, 10 ± 3 mg, 12 ± 3 mg, 15 ± 3 mg, 22 ± 4 mg, 27 ± 4 mg, 30 ± 5 mg, 35 ± 5 mg, 40 ± 5 mg 50 ± 5 mg, 60 ±10 mg, 75 ± 10 mg, 85 ± 10 mg, 100 ± 15 mg, 125 ± 20 mg, 150 ± 25 mg, or 200 ± 25 mg of seletracetam.

In certain embodiments, the unit dosage form when placed in 1 mL of unbuffered water at pH 7 results in a solution having a pH of between 5.4 and 9.1 (e.g., a pH of between 5.4 and 8.8, 5.4 and 8.3, 6.0 and 8.8, 6.0 and 8.5, 6.5 and 8.5, 7.0 and 8.5, 7.2 and 8.2, 7.4 and 8.0, 7.6 and 8.5, 8.2 and 8.5, 8.4 and 8.7, 8.6 and 8.8, or 8.7 and 9.1).

In some embodiments, following sublingual or buccal administration to a subject, the unit dosage form produces an average circulating plasma or serum concentration of seletracetam of at least 50 ng/mL within a period of from 2 to 30 minutes following the administration. In certain embodiments, the unit dosage form can produce an average circulating concentration ranging from 40 to 100 ng/mL within 2 to 7 minutes, from 60 to 150 ng/mL within 2 to 7 minutes, from 80 to 200 ng/mL within 2 to 7 minutes, from 150 to 300 ng/mL within 2 to 7 minutes, from 200 to 500 ng/mL within 2 to 7 minutes, from 400 to 1000 ng/ml within 2 to 7 minutes, from 40 to 100 ng/mL within 5 to 10 minutes, from 60 to 150 ng/mL within 5 to 10 minutes, from 80 to 200 ng/mL within 5 to 10 minutes, from 150 to 300 ng/mL within 5 to 10 minutes, from 200 to 500 ng/mL within 5 to 10 minutes, from 400 to 1000 ng/ml within 5 to 10 minutes, from 40 to 100 ng/mL within 7 to 15 minutes, from 60 to 150 ng/mL within 7 to 15 minutes, from 80 to 200

ng/mL within 7 to 15 minutes, from 150 to 300 ng/mL within 7 to 15 minutes, from 200 to 500 ng/mL within 7 to 15 minutes, from 400 to 1000 ng/ml within 7 to 15 minutes,from 40 to 100 ng/mL within 15 to 30 minutes, from 60 to 150 ng/mL within 15 to 30 minutes, from 80 to 200 ng/mL within 15 to 30 minutes, from 150 to 300 ng/mL within 15 to 30 minutes, from 200 to 500 ng/mL within 15 to 30 minutes, from 400 to 1000 ng/ml within 15 to 30 minutes, following the administration In some embodiments, the unit dosage form can produce an average circulating concentration ranging from 20 to 40 ng/mL within 7 to 10 minutes, from 30 to 60 ng/mL within 5 to 10 minutes, from 40 to 100 ng/mL within 5 to 10 minutes, from 75 to 150 ng/mL within 5 to 10 minutes, from 20 to 40 ng/mL within 7 to 15 minutes, from 30 to 60 ng/mL within 7 to 15 minutes, from 40 to 100 ng/mL within 7 to 15 minutes, from 75 to 150 ng/mL within 7 to 15 minutes, from 20 to 40 ng/mL within 15 to 20 minutes, from 30 to 60 ng/mL within 15 to 20 minutes, from 50 to 100 ng/mL within 15 to 20 minutes, or from 75 to 150 ng/mL within 15 to 20 minutes following the administration.

In certain aspects, an orally disintegrating tablet comprising seletracetam is provided. In some embodiments, the orally disintegrating tablet comprises a matrix material and seletracetam for buccal or sublingual administration. In certain embodiments, the orally disintegrating tablet is administered buccally. In some embodiments, the orally disintegrating tablet is placed inside the central portion of the upper lip, between the inside of the lip and gums, directly below the nose. In certain embodiments, the orally disintegrating tablet is administered sublingually. In some embodiments, the orally disintegrating tablet disintegrates within 20 seconds after being placed in the oral cavity of the subject.

The formulation may comprise an alkyl saccharide such as tetradecyl maltoside or dodecyl maltoside as described in U.S. Patent No. 9,283,280 or may be manufactured without the alkyl saccharide. The formulation may reach a therapeutic plasma level in substantially less time than, and a first-pass effect substantially less than that observed for an equivalent oral formulation. In some embodiments, the formulation comprises about 0.1% to 10% alkylsaccharide, and reaches therapeutic plasma levels within less than 1 hour after sublingual or buccal administration and a first-pass effect of less than 40% compared to oral administration. The alkylglycoside may be any suitable alykylglycoside. In certain embodiments, the alkylglycoside is dodecyl maltoside, tetradecylm altoside, sucrose dodecanoate, or sucrose mono- and di-stearate. The formulation may include seletracetam at a unit dose of 1 to 300 mg

(e.g., 1 to 200 mg) per unit. For children including newborn or even preterm babies, the unit dosage form may comprise a dose of 0.1 to 20 mg per unit.

Further, it has been discovered that when certain types of orally disintegrating tablets are placed between the cheek and gum or into close association with buccal tissue inside the mouth, an even larger proportion of the drug is directly absorbed into the systemic circulation and a smaller amount subsequently undergoes first-pass elimination in the liver. Lastly, it has been discovered that a desirable location within the mouth for this effect may be inside the central portion of the upper lip, between the inside of the lip and gums, directly below the nose. In some aspects, these types of orally disintegrating tablets are prepared by lyophilization or vacuum drying. In certain aspects, the dosage formulation is prepared in a manner that results in a dosage formulation that is substantially porous.

In certain embodiments, the formulation comprises an orally disintegrating tablet for sublingual or buccal administration. In some embodiments, the orally disintegrating tablet comprises a network of the active ingredient and a water-soluble or water-dispersible carrier matrix, which is inert towards the active ingredient and excipients. In various embodiments, the network may be obtained by lyophilizing or subliming solvent from a formulation in the solid state, which formulation comprises the active ingredient seletracetam, an alkyl saccharide, and a solution of the carrier in a solvent. In certain embodiments, the alkyl saccharide is omitted if adequate absorption rate is achieved without the alkyl saccharide. In certain embodiments, the solvent comprises water. Water—alcohol mixtures may also be employed where drug solubility in the mixed solvent is enhanced. To achieve high concentrations of the active drug seletracetam in the formulation (e.g. 100 to up to 300 mg or 50 to 200 mg per unit dosage form), dispersions of small drug particles (micronized seletracetam particles, e.g. micronized seletracetam co-crystal particles) may be suspended in an aqueous gel that maintains uniform distribution of the insoluble fraction of seletracetam during the lyophilization or subliming process. In certain embodiments, the use of suspensions instead of solutions limits the final volume of the unit dosage form to a minimum, which increases the acceptability of the dosage form.

In some embodiments, an aqueous gel may be formed using selected alkyl saccharides such as sucrose mono- and di-stearate and/or tetradecyl-maltoside similar to the self-assembling hydrogels described in U.S. Patent Application No. 60/957,960, incorporated herein by reference. In some embodiments, any pharmaceutically acceptable gel forming agent including

cellulose derivatives, alginates and alike gel forming agents as described below may also be suitable. In various aspects, the orally disintegrating tablet disintegrates within 20 seconds (e.g. less than 10 seconds), after being placed in the oral cavity. In some embodiments, matrix-forming agents suitable for use in the orally disintegrating tablet include materials derived from animal or vegetable proteins, such as the gelatins, collagens, dextrins and soy, wheat and psyllium seed proteins; gums such as acacia, guar, agar, and xanthan, polysaccharides; alginates; carrageenans; dextrans; carboxymethylcelluloses; pectins; synthetic polymers such as polyvinylpyrrolidone; hyaluronic acid polymer; and polypeptide/protein or polysaccharide complexes such as gelatin-acacia complexes. In some embodiments, gelatin, particularly fish gelatin or porcine gelatin is used. The dose of seletracetam incorporated in each unit formulation may be in the range of 1 to 300 mg/unit dosage form (e.g., 1 to 200 mg/unit dosage form) and may be included as seletracetam or any seletracetam co-crystal dissolved or suspended in the aqueous vehicle.

In some embodiments, the therapeutic compositions comprise a pharmaceutically acceptable carrier. The pharmaceutically acceptable carrier may be an aqueous or non-aqueous agent, for example, alcoholic or oleaginous, or a mixture thereof, and may contain a surfactant, emollient, lubricant, stabilizer, dye, perfume, preservative, acid, or base for adjustment of pH, a solvent, emulsifier, gelling agent, moisturizer, stabilizer, wetting agent, buffering agent, humectant, or other component commonly included in a particular form of the pharmaceutical composition. Pharmaceutically acceptable carriers are well known in the art and include, for example, aqueous solutions such as water or physiologically buffered saline (phosphate buffer, acetate buffer, citrate buffer, or alike) or other solvents or vehicles such as glycols, glycerol, and oils such as olive oil or injectable organic esters. A pharmaceutically acceptable carrier can contain physiologically acceptable compounds that act, for example, to stabilize or to increase the absorption of the specific inhibitor, for example, carbohydrates, such as glucose, sucrose or dextrans, antioxidants, such as ascorbic acid or glutathione, chelating agents, low molecular weight proteins or other stabilizers or excipients. A pharmaceutically acceptable carrier can also be selected from substances such as distilled water, benzyl alcohol, lactose, starches, talc, magnesium stearate, polyvinylpyrrolidone, alginic acid, colloidal silica, titanium dioxide, and flavoring agents.

Intranasal Formulations

In some embodiments, seletracetam is prepared as an intranasal liquid formulation.

In some embodiments, this intranasal liquid formulation can be also administered buccally or sublingually.

In some embodiments, the intranasal formulation is an aqueous seletracetam solution comprising seletracetam at a concentration of 1-1200 mg/mL (e.g., 1-350 mg/mL). In other embodiments, the seletracetam may be suspended in an aqueous solution at a concentration exceeding the water solubility of seletracetam. In certain embodiments, the formulation comprising seletracetam is an intranasal formulation that comprises about 20-1000 mg/mL (e.g., 20-200 mg/mL) seletracetam in about 0.9% saline. For use in children, neonates, and preterm neonates, the concentration of the formulation may be lower, e.g. 10-100 mg/ml, or the volume of administration is reduced to 5-50 µl, to allow for a lower unit dose as compared to adults.

In some embodiments, an aqueous formulation comprises seletracetam and a pharmaceutically acceptable excipient (e.g., in water or saline or buffered saline (phosphate buffer, acetate buffer, citrate buffer or alike)). In certain embodiments, the formulation comprises seletracetam at a concentration of 25 mg/mL to 800 mg/mL. In some embodiments, the formulation comprises seletracetam at a concentration of about 50 mg/mL, about 100 mg/mL, about 200 mg/mL, about 250 mg/mL, about 400 mg/mL, about 500 mg/mL, or about 600 mg/mL. In certain embodiments, the formulation comprises seletracetam at a concentration of about 5 mg/mL, about 7.5 mg/ml; about 10 mg/mL; about 12.5 mg/ml; about 15 mg/mL; about 17.5 mg/ml; about 20 mg/mL; about 25 mg/mL; about 30 mg/mL; about 35 mg/mL; about 40 mg/mL; about 45 mg/mL; about 50 mg/mL, about 75 mg/ml, about 100 mg/ml, about 150 mg/ml, about 200 mg/ml, about 250 mg/ml, about 300 mg/ml, about 400 mg/ml, about 500 mg/ml, about 600 mg/ml, about 700 mg/ml, about 800 mg/ml, about 900 mg/mL, about 1,000 mg/ml, about 1,100 mg/mL, or about 1,200 mg/ml. For small children or neonates including preterm or low birthweight neonates, the concentration of seletracetam in the formulation may even be lower, i.e. about 1 mg/ml, about 3 mg/ml, or about 4 mg/ml. In any of the compositions described herein, the seletracetam composition is a sterile composition, either achieved by sterile filtration or by adequate autoclaving procedures, or it is a composition with controlled low microbiological contamination level, manufactured in controlled clean room environment, suitable for intranasal administration.

In some embodiments, the formulation comprises seletracetam at a concentration of 1 mg/ml to 1,200 mg/ml, 1 mg/ml to 1,000 mg/ml, 1 mg/ml to 800 mg/ml, 1 mg/ml to 600 mg/ml, 1 mg/ml to 400 mg/ml, 1 mg/ml to 200 mg/ml, 1 mg/ml to 100 mg/ml, 1 mg/ml to 50 mg/ml, 1 mg/ml to 30 mg/ml, 1 mg/ml to 20 mg/ml, 1 mg/ml to 10 mg/ml, 1 mg/ml to 5 mg/ml, 5 mg/ml to 1,200 mg/ml, 5 mg/ml to 1,000 mg/ml, 5 mg/ml to 800 mg/ml, 5 mg/ml to 600 mg/ml, 5 mg/ml to 400 mg/ml, 5 mg/ml to 200 mg/ml, 5 mg/ml to 100 mg/ml, 5 mg/ml to 50 mg/ml, 5 mg/ml to 30 mg/ml, 5 mg/ml to 20 mg/ml, 5 mg/ml to 10 mg/ml, 10 mg/ml to 1,200 mg/ml, 10 mg/ml to 1,000 mg/ml, 10 mg/ml to 800 mg/ml, 10 mg/ml to 600 mg/ml, 10 mg/ml to 400 mg/ml, 10 mg/ml to 200 mg/ml, 10 mg/ml to 100 mg/ml, 10 mg/ml to 50 mg/ml, 10 mg/ml to 30 mg/ml, 10 mg/ml to 20 mg/ml, 20 mg/ml to 1,200 mg/ml, 20 mg/ml to 1,000 mg/ml, 20 mg/ml to 800 mg/ml, 20 mg/ml to 600 mg/ml, 20 mg/ml to 400 mg/ml, 20 mg/ml to 200 mg/ml, 20 mg/ml to 100 mg/ml, 20 mg/ml to 50 mg/ml, 20 mg/ml to 30 mg/ml, 30 mg/ml to 1,200 mg/ml, 30 mg/ml to 1,000 mg/ml, 30 mg/ml to 800 mg/ml, 30 mg/ml to 600 mg/ml, 30 mg/ml to 400 mg/ml, 30 mg/ml to 200 mg/ml, 30 mg/ml to 100 mg/ml, 30 mg/ml to 50 mg/ml, 50 mg/ml to 1,200 mg/ml, 50 mg/ml to 1,000 mg/ml, 50 mg/ml to 800 mg/ml, 50 mg/ml to 600 mg/ml, 50 mg/ml to 400 mg/ml, 50 mg/ml to 200 mg/ml, 50 mg/ml to 100 mg/ml, 100 mg/ml to 1,200 mg/ml, 100 mg/ml to 1,000 mg/ml, 100 mg/ml to 800 mg/ml, 100 mg/ml to 600 mg/ml, 100 mg/ml to 400 mg/ml, 100 mg/ml to 200 mg/ml, 200 mg/ml to 1,200 mg/ml, 200 mg/ml to 1,000 mg/ml, 200 mg/ml to 800 mg/ml, 200 mg/ml to 600 mg/ml, 200 mg/ml to 400 mg/ml, 400 mg/ml to 1,200 mg/ml, 400 mg/ml to 1,000 mg/ml, 400 mg/ml to 800 mg/ml, 400 mg/ml to 600 mg/ml, 600 mg/ml to 1,200 mg/ml, 600 mg/ml to 1,000 mg/ml, 600 mg/ml to 800 mg/ml, 800 mg/ml to 1,200 mg/ml, 800 mg/ml to 1,000 mg/ml, or 1,000 mg/ml to 1,200 mg/ml. In preferred embodiments, the formulation comprises seletracetam at a concentration of 50 mg/ml to 600 mg/ml. In more preferred embodiments, the formulation comprises seletracetam at a concentration of about 100 mg/ml, or about 150 mg/ml, or about 200 mg/ml, or about 250 mg/ml.

In certain embodiments, seletracetam and pharmaceutically acceptable excipients are combined to increase the solubility and stability of seletracetam in aqueous media. Such excipients may include ethanol, propylene glycol, polyethylene glycol, polysorbate 80, meglumine, and alike. In such formulations, seletracetam may be contained at a concentration of about 50 mg/mL, about 60 mg/ml; about 75 mg/mL; about 100 mg/ml; about 125 mg/mL; about

150 mg/ml; about 175 mg/mL; about 200 mg/mL; about 225 mg/mL; about 250 mg/ml, about 300 mg/ml, about 350 mg/ml, about 400 mg/ml, about 500 mg/ml, about 600 mg/ml, about 700 mg/ml, about 800 mg/ml, about 1,000 mg/ml, or about 1,200 mg/ml. In embodiments, the formulation comprising seletracetam is sterile, or manufactured in a controlled environment with a controlled low microbiological contamination level.

In some embodiments, the seletracetam formulations described herein may further comprise pharmaceutically compatible carrier materials such as solvents (e.g., ethanol), oils (e.g., edible oils), suspending agents, surfactants, solubilizers, stabilizers, lubricants, wetting agents, diluents, preservatives, and the like.

In certain embodiments, the formulation described herein comprises a water soluble polymer. The water soluble polymer may serve as a mucoadhesive agent. In certain embodiments, the water soluble polymer is selected from methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl ethylcellulose, sodium carboxymethylcellulose, polyvinyl alcohol, polyvinyl pyrrolidone, polyethylene glycol, poly(methyl methacrylate), polycarbophil, gelatin, alginate, poly(acrylic acid), polyethylene oxide, hyaluronic acid polymers, including but not limited to hyaluronic acid polymer with a molecular weight of about 3,000 Dalton, or about 10,000 Dalton, or about 25,000 Dalton, or about 50,000 Dalton, or about 100,000 Dalton, or about 350,000 Dalton, or about 1,000,000 Dalton, or about 3,000,000 Dalton, and chitosan, or a derivative thereof.

In some embodiments, the formulation described herein comprises a surfactant. In certain embodiments, the surfactant is anionic, cationic or non-ionic. In some embodiments, the surfactant is polysorbate 80 and 20, polyethylene glycol esters, polyethylene glycols, glycerol ethers, glyceryl monoleate, lecithin or mixtures of those compounds.

In certain embodiments, the formulation described herein comprises a co-solvent. In some embodiments, the co-solvent comprises a monohydric alcohol or a polyhydric alcohol (e.g. polyethylene glycol, polypropyleneglycol, and the like).

In certain embodiments, the formulation comprises a humectant. In some embodiments, the humectant comprises glycerin, sorbitol, dexpanthenol, or mannitol.

The formulation described herein may comprise a chelating agent such as disodium salt of edetate. The formulation may comprise a suitable water-soluble polymer. In some embodiments, the water-soluble polymer comprises methylcellulose, hydroxyethyl cellulose,

hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl ethylcellulose, sodium carboxymethylcellulose, polyvinyl alcohol, polyvinylpyrrolidone, polyethylene glycol, poly(methyl methacrylate), polycarbophil, gelatin, alginate, poly(acrylic acid), polyethylene oxide, hyaluronic acid polymer including but not limited to hyaluronic acid polymer with a molecular weight of about 3,000 Dalton, or about 10,000 Dalton, or about 25,000 Dalton, or about 50,000 Dalton, or about 100,000 Dalton, or about 350,000 Dalton, or about 1,000,000 Dalton, or about 3,000,000 Dalton, chitosan, or a derivative thereof.

In certain embodiments, the formulation described herein comprises a stabilizing agent. In some embodiments, the stabalizing agent comprises sodium hydrogen sulfite, glycerin, sodium citrate, butyl hydroxyanisole, benzalkonium chloride, edetic acid and pharmaceutically acceptable salts thereof, tocopherol, or derivatives thereof, optionally in combination with sodium edetate.

In certain embodiments, the formulation described herein comprises an isotonizing agent. In some embodiments, the isotizing agent comprises sodium chloride, potassium chloride, ethanol, D-mannitol, glucose, glycerol, glycine, glycerin, dextrose, glyceryl dioleate, xylitol, propylene, or propylene glycol.

In certain embodiments, the formulation described herein comprises a buffering agent. In some embodiments, the buffering agent is an acid (e.g. hydrochloric acid, acetic acid, and citric acid). In certain embodiments, the buffering agent comprises sodium hydroxide, or a sodium or potassium salt (e.g., sodium citrate, sodium carbonate, sodium tetraborate, sodium phosphate, sodium acetate, sodium bicarbonate, potassium hydrogen phosphate, or potassium phosphate).

In some embodiments, the formulation described herein comprises a thickening agent. In some embodiments, the thickening agent is methylcellulose, ethyl cellulose, microcrystalline cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose (e.g., Natrosol™ 250 M), sodium carboxymethylcellulose, polyvinyl pyrrolidone, polyvinyl alcohol, sodium chondroitin sulfate, sodium hyaluronate, chitosan, or hyaluronic acid. In certain embodiments, the hyaluronic acid is a hyaluronic acid polymer having a molecular weight of about 3,000 Dalton, about 10,000 Dalton, about 25,000 Dalton, about 50,000 Dalton, about 100,000 Dalton, about 350,000 Dalton, about 1,000,000 Dalton, or about 3,000,000 Dalton.

In some embodiments, the formulation comprises hydroxyethyl cellulose (e.g., Natrosol™ 250 M) at a concentration of 0.2% w/w to 10% w/w, 0.5% w/w to 5% w/w, 0.5%

w/w to 2% w/w, 0.5% w/w to 1.5% w/w, about 0.75% w/w, or about 1% w/w. In preferred embodiments, the formulation comprises 0.5% w/w to 2% w/w of the hydroxyethyl cellulose. In more preferred embodiments, the formulation comprises about 0.75% w/w of the hydroxyethyl cellulose.

In certain embodiments, the formulation described herein comprises a penetration enhancer. In some embodiments, the penetration enhancer comprises chitosan, chitosan derivatives, cyclodextrin, bile salts such as taurodeoxycholate, liposomes, starch microspheres, propylene glycol, or glycyrrhizin. In certain embodiments, the formulation comprises about 0.1% to 10% alkyl saccharide. In some embodiments, the alkyl saccharide is dodecyl maltoside, tetradecyl maltoside, sucrose dodecanoate, or sucrose mono- and di-stearate.

In certain embodiments, the formulation described herein reaches therapeutic plasma levels within less than 45 min (e.g., less than 30 min) after intranasal administration. In certain embodiments, the formulation described herein reaches therapeutic plasma levels within less than 15 min after intranasal administration. In some embodiments, the formulations described herein exhibit a first-pass effect of less than 40% compared to oral administration.

In some embodiments, the formulation described herein comprises a flavor modifier. In certain embodiments, the flavor modifier comprises menthol, saccharin sodium, or sorbitol. In certain embodiments, the formulation described herein comprises an electrolyte. In some embodiments, the electrolyte comprises sodium chloride or potassium chloride.

In some embodiments, the formulation described herein comprises a commercially available excipient. In some embodiments, the commercially available excipient is Kollidon®l2 PF, Kollidon® 17 PF, Kolliphor® EL, 20 Kolliphor® ELP, or Kolliphor® HS 15 (BASF).

In some embodiments, the formulation described herein is an oil-based suspension, an emulsion, or a solution. In certain embodiments, the formulation described herein is an aqueous suspension, an aqueous emulsion, or an aqueous solution. In some embodiments, the formulation described herein comprises a seletracetam solubilizing and stabilizing excipient such as ethanol, or one or more cyclodextrins. In certain embodiments, the formulation described herein does not comprise seletracetam solubilizing excipients such as ethanol or one or more cyclodextrins. In certain embodiments, neat seletracetam or seletracetam-co crystal powder may be insufflated into the nose. In some embodiments, the formulation described herein comprises an oil. In some embodiments, the oil comprises canola oil, miglyol oil, peanut oil, or mixtures thereof. In certain

embodiments, the formulation described herein is administered intranasally at a dose of seletracetam in the range of about 1 mg to about 300 mg (e.g., about 1 mg to about 250 mg) per administration for an adult or at a dose of 0.02 mg/kg to 6 mg/kg (e.g., 0.02 mg/kg to 5 mg/kg).

In some embodiments, the formulation comprising seletracetam is administered intranasally at a dose of seletracetam in the range of about 0.1 mg/kg to about 12 mg/kg (e.g., about 0.1 mg/kg to about 10 mg/kg). In certain embodiments, the dose of seletracetam is achieved by single administration to one nostril, by administering up to 3 metered doses per nostril, or by repeated administration of multiple, up to 10 doses to one or both nostrils within less than 1 hour. In some embodiments, the volume of one metered dose administered ranges from 10 µl to 200 µl, 25 to 160 µl, or 25 µl to 100 µl. In some embodiments, such as for the administration to young children or neonates including preterm neonates or low birth weight neonates, the volume is 10 to 75 µl (e.g., 10 to 50 µl) per metered dose.

In some aspects, a nasal spray device comprising seletracetam is provided. In certain embodiments, the nasal spray device comprises a pharmaceutical formulation comprising the seletracetam and a pharmaceutically acceptable liquid carrier. In certain embodiments, the liquid comprises water. The nasal spray device may be any device configured to dispense a spray into a nasal cavity of a subject. In some embodiments, the nasal spray device comprises a vial, a piston, a swirl chamber, and the formulation. In certain embodiments, a spray is formed when the formulation is forced out through the swirl chamber. In some embodiments, the nasal spray device is hand actuated. In certain embodiments, the nasal spray device is actuated by nasal inhalation. In some embodiments, the nasal spray device is actuated electrically.

In certain embodiments, the nasal spray device is a unit-dose device, i.e., the nasal spray device is configured to dispense a single dose of seletracetam. In some embodiments, the nasal spray device is a bi-dose device or multi-dose device. In some embodiments, the nasal spray device is a bi-dose device. In certain embodiments, the nasal spray device is a multi-dose device. In some embodiments, the nasal spray device comprises a mechanical spray pump. In certain embodiments, the nasal spray device comprises a metered spray pump. In certain embodiments, the nasal spray device is configured for self-administration. In some embodiments, the device is equipped with silver particles or silver lining in the outlet path to prevent or reduce bacterial contamination. In some embodiments, the device is configured to dispense 25 µL to 200 µL of the formulation described herein per spray actuation. In certain embodiments, the device is

configured to dispense about 50 µL, about 75 µL, about 100 µL, about 160 µL, or about 200 µL of the formulation described herein per spray actuation. In preferred embodiments, the device is configured to dispense about 100 µL of the formulation described herein per spray actuation.

In certain aspects, an oromucosal spray device comprising seletracetam is provided. In certain embodiments, the oromucosal spray device comprises a pharmaceutical formulation comprising the seletracetam and a pharmaceutically acceptable liquid carrier. In certain embodiments, the liquid comprises water. The oromucosal spray device may be any device configured to dispense a spray into a subject's oral mucosa. In some embodiments, the oromucosal spray device comprises a vial, a piston, a swirl chamber, and the formulation. In certain embodiments, a spray is formed when the formulation is forced out through the swirl chamber. In some embodiments, the oromucosal spray device is hand actuated. In certain embodiments, the oromucosal spray device is actuated by nasal inhalation. In some embodiments, the oromucosal spray device is actuated electrically.

In certain embodiments, the oromucosal spray device is a unit-dose device, i.e., the oromucosal spray device is configured to dispense a single dose of seletracetam. In some embodiments, oromucosal spray device is a bi-dose device or multi-dose device. In certain embodiments, the oromucosal spray device is a multi-dose device. In some embodiments, the oromucosal spray device comprises a mechanical spray pump. In certain embodiments, the oromucosal spray device comprises a metered spray pump. In certain embodiments, the oromucosal spray device is configured for self-administration. In some embodiments, the device is equipped with silver particles or silver lining in the outlet path to prevent or reduce bacterial contamination. In some embodiments, the device is configured to dispense 25 µL to 200 µL of the formulation described herein per spray actuation. In certain embodiments, the device is configured to dispense about 50 µL, about 75 µL, about 100 µL, about 160 µL, or about 200 µL of the formulation described herein per spray actuation. In preferred embodiments, the device is configured to dispense about 100 µL of the formulation described herein per spray actuation.

In certain embodiments, the device is a metered dose device. In even further embodiments, the metered dose device is configured to dispense equal metered doses in the range of 25 µL to 200 µL per spray actuation. Metered doses may be about 50 µL, about 75 µL, about 100 µL, or about 160 µL per spray actuation.

In certain embodiments, the device is a metered dose device designed for intranasal spray delivery with a straight upwards directed outlet. In other embodiments, the device is a metered dose device designed for oromucosal (buccal, sublingual) delivery, e.g. with a bent outlet for oromucosal delivery.

In some embodiments, the formulation described herein is administered 1 to 10 times over a period of 1 to 10 minutes. In certain embodiments, the formulation comprising seletracetam is administered intranasally 1 to 5 times in each nostril over a period of 1 to 10 minutes. In some embodiments, the formulation described herein is administered 1 to 5 times over a period of 1 to 5 minutes, or 1 to 3 minutes.

In some embodiments, the formulation is administered by spraying it directly into the mouth or under the tongue (sublingual) or in the cheeks or onto the inner surface of the lips in the space between teeth and lips instead of intranasally, resulting in an exposure of the oromucosal mucosa (i.e., oromucosal administration). This route results in absorption via the oral (including buccal, lingual, or sublingual) mucosa.

In certain embodiments, following intranasal or oromucosal administration of the formulation described herein to a subject, an average circulating plasma or serum concentration of seletracetam of at least 25 ng/mL (e.g., at least 50 ng/mL) within a period of from 2 to 30 minutes (e.g., from 5 to 15 minutes) is achieved. In some embodiments, the unit dosage form produces an average circulating concentration ranging from 40 to 100 ng/mL within 2 to 7 minutes, from 60 to 150 ng/mL within 2 to 7 minutes, from 80 to 200 ng/mL within 2 to 7 minutes, from 150 to 300 ng/mL within 2 to 7 minutes, from 200 to 500 ng/mL within 2 to 7 minutes, from 400 to 1000 ng/ml within 2 to 7 minutes, from 40 to 100 ng/mL within 5 to 10 minutes, from 60 to 150 ng/mL within 5 to 10 minutes, from 80 to 200 ng/mL within 5 to 10 minutes, from 150 to 300 ng/mL within 5 to 10 minutes, from 200 to 500 ng/mL within 5 to 10 minutes, from 400 to 1000 ng/ml within 5 to 10 minutes, from 40 to 100 ng/mL within 7 to 15 minutes, from 60 to 150 ng/mL within 7 to 15 minutes, from 80 to 200 ng/mL within 7 to 15 minutes, from 150 to 300 ng/mL within 7 to 15 minutes, from 200 to 500 ng/mL within 7 to 15 minutes, from 400 to 1000 ng/ml within 7 to 15 minutes, from 40 to 100 ng/mL within 15 to 30 minutes, from 60 to 150 ng/mL within 15 to 30 minutes, from 80 to 200 ng/mL within 15 to 30 minutes, from 150 to 300 ng/mL within 15 to 30 minutes, from 200 to 500 ng/mL within 15 to 30 minutes, from 400 to 1000 ng/ml within 15 to 30 minutes, following the administration. In

certain embodiments, the formulation produces an average circulating concentration ranging from 20 to 40 ng/mL within 7 to 10 minutes, from 30 to 60 ng/mL within 5 to 10 minutes, from 40 to 100 ng/mL within 5 to 10 minutes, from 75 to 150 ng/mL within 5 to 10 minutes, from 20 to 40 ng/mL within 7 to 15 minutes, from 30 to 60 ng/mL within 7 to 15 minutes, from 40 to 100 ng/mL within 7 to 15 minutes, from 75 to 150 ng/mL within 7 to 15 minutes, from 20 to 40 ng/mL within 15 to 20 minutes, from 30 to 60 ng/mL within 15 to 20 minutes, from 50 to 100 ng/mL within 15 to 20 minutes, or from 75 to 150 ng/mL within 15 to 20 minutes following administration.

In some embodiments, an efficacious or effective amount of seletracetam is determined by first administering a low dose or small amount of the agent and then incrementally increasing the administered dose or dosages, until a desired effect is observed in the treated subject with minimal or no toxic side effects. In some patients, very low plasma levels as low as 5 ng/ml have been shown to result in a desired pharmacodynamic (e.g. antiseizure) effect [Trenité, Dorothee Kasteleijn-Nolst, et al. "A multicenter Phase II randomized, placebo-controlled single-blind trial with the SV2A ligand seletracetam in photosensitive epilepsy patients." Epilepsy & Behavior 164 (2025): 110241]. Thus, in such instances, an about 2-fold, 5-fold or 10-fold lower dose can be administered, resulting in about 2-fold, 5-fold or 10-fold lower plasma levels, but with the same speed of absorption after intranasal or buccal or sublingual or oromucosal administration.

In some embodiments, the formulation described herein is administered so as to deliver a first bolus dose or a series of bolus doses; followed by administration of a second/maintenance dosing regimen; wherein, the administration of said second dosing regimen occurs at intervals of 1 to 24 h as once daily, twice daily, three times daily or up to 5 times daily administration for 1-6 days, or longer; and administration of a third downward taper dosing regimen, wherein, the administration of said third downward taper dosing regimen occurs at intervals over 10-100 hours; wherein, collectively, the administrations are provided in sufficient amount to treat a subject suffering from any condition described herein. In some embodiments, the bolus dose may be 0.75x, the second/maintenance dosing regimen may comprise doses of 0.5x or lower, and the taper dosing regimen may comprise doses of 0.25x or lower. In some embodiments, following a well tolereated first bolus dose, the maintenance dose may be maintained or even increased and not reduced, i.e. the maintenance dose may be 1,2,3,4,5, 10, 20 x higher than the initial dose. Tapering doses may follow, if needed.

In some embodiments, a subject is administered a dose of a formulation described herein prophylactically (e.g., prior to onset of symptoms such as, for example, seizures, or during a seizure related aura preceding the start of a seizure, or following seizure risk detection by a seizure detection device). In certain embodiments, the formulation described herein is administered in multiple doses over a period of minutes to an hour, e.g., 1-5 doses over about 1 to 10 minutes, over about 1 to 5 minutes, over about 1-3 minutes, or over about 1 to 30 minutes or over about 1 to 60 minutes, to achieve therapeutic doses.

In some embodiments, a method of treating epilepsy in a subject in need thereof comprises sublingually or buccally administering a formulation described herein to the subject. In certain embodiments, a method for treating seizures and seizure-associated symptoms or pain in a subject in need thereof comprises administering a formulation described herein to the subject. In some embodiments, the pain comprises neuropathic pain, neuralgia, chronic pain, peripheral nerve pain, or migraine, in a subject afflicted with epilepsy or suffering from symptomatic seizures or suffering from any kind of pain, by sublingually or buccally administering a formulation described herein in an amount effective to alleviate the seizures or the symptoms of pain.

In certain embodiments, a method for treating a pain in a subject in need thereof comprises administering a formulation described herein to the subject. In some embodiments, the pain comprises neuropathic pain, neuralgia, chronic pain, peripheral nerve pain, or migraine.

In certain embodiments, a method for treating a cognitive impairment or dementia (e.g., Alzheimer's disease) in a subject in need thereof comprises administering a formulation described herein to the subject. In some embodiments, the cognitive impairment comprises Mild Cognitive Impairment (MCI), Age-related Cognitive Decline (ARCD) or Age-Associated Memory Impairment (AAMI). Related treatment methods comprising administration of seletracetam are described, for example, in US Patent Application Publication No. 2024/0293363 A1, which is incorporated by reference herein.

In some embodiments, seletracetam can be administered as an aqueous intranasal spray formulation. In certain embodiments, the intranasal formulation is an aqueous seletracetam solution comprising seletracetam at a concentration of 1-1200 mg/mL (e.g., 1-250 mg/ml) of seletracetam. In some embodiments, the seletracetam is suspended in an aqueous solution at a concentration exceeding the water solubility of seletracetam, i.e. at a concentration exceeding

1200 mg/ml. In some embodiments, the composition comprising seletracetam is an intranasal composition that comprises about 10-1000 mg/mL seletracetam in about 0.9% saline.

In some embodiments, an aqueous formulation comprises seletracetam and a pharmaceutically acceptable excipient (e.g., in water or saline or buffered saline (phosphate buffer, acetate buffer, citrate buffer or alike)) comprising seletracetam at a concentration of about 5 mg/mL, about 7.5 mg/ml; about 10 mg/mL; about 12.5 mg/ml; about 15 mg/mL; about 17.5 mg/ml; about 20 mg/mL; about 25 mg/mL; about 30 mg/mL; about 35 mg/mL; about 40 mg/mL; about 45 mg/mL; about 50 mg/mL, about 75 mg/ml, about 100 mg/ml, about 150 mg/ml, about 200 mg/ml; about 225 mg/ml; about 250 mg/ml; about 275 mg/ml about 300 mg/ml, about 350 mg/ml, about 400 mg/ml, about 450 mg/ml, about 500 mg/ml, about 600 mg/ml, about 700 mg/ml, about 800 mg/ml, about 900 mg/ml, about 1000 mg/ml, or about 1200 mg/ml. In some embodiments, the formulation comprising seletracetam composition is a sterile composition, either achieved by sterile filtration or by adequate autoclaving procedures. In some other embodiments, the formulation comprising seletracetam composition is a composition with controlled microbiological contamination or as sterile composition, as achieved by a manufacturing process conducted in a controlled environment, e.g. applying a clean room manufacturing process, conducted in a class A or class B clean room environment.

In certain embodiments, seletracetam and pharmaceutically acceptable excipients are combined to increase the solubility and/or stability of seletracetam in aqueous media. Such excipients include but are not limited to ethanol, propylene glycol, polyethylene glycol, polysorbate 80, meglumine, and alike. In such formulations, seletracetam is contained at a concentration of about 50 mg/mL, about 60 mg/ml; about 75 mg/mL; about 100 mg/ml; about 125 mg/mL; about 150 mg/ml; about 175 mg/mL; about 200 mg/mL; about 225 mg/mL; about 250 mg/mL; about 275 mg/mL; about 300 mg/mL, about 350 mg/ml, about 400 mg/ml, about 450 mg/ml, about 500 mg/ml, about 600 mg/ml, about 700 mg/ml, about 800 mg/ml, about 900 mg/ml, about 1000 mg/ml, or about 1200 mg/ml. In certain embodiments, the formulation comprising seletracetam is sterile. In some other embodiments, the formulation comprising seletracetam composition is a composition with controlled microbiological contamination or as a sterile composition, as achieved by a manufacturing process conducted in a controlled environment, e.g. applying a clean room manufacturing process, conducted in a class A or class B clean room environment.

In some embodiments, the seletracetam compositions described herein may further comprise pharmaceutically compatible carrier materials such as solvents (e.g., ethanol), oils (e.g., edible oils), suspending agents, surfactants, solubilizers, stabilizers, lubricants, wetting agents, diluents, preservatives, and the like.

In certain embodiments, the intranasal or oromucosal formulations are prepared for repeated intranasal or oromucosal administration by use of a metered dose administration device. In some embodiments, the formulation needs to contain preservatives to prevent/reduce bacterial growth and the risk of bacterial growth in the formulation and on the surface of the administration device. In some embodiments, the antimicrobial preservative is selected from the group consisting of: benzalkonium chloride, methylparaben, sodium benzoate, benzoic acid, phenyl ethyl alcohol, mixtures thereof, and the like. In certain embodiments, the formulation comprises about 0.01 % to about 0.50% (w/w), more preferably about 0.08% to about 0.40% (w/w), and most preferably about 0.10% to about 0.30% (w/w), of the antimicrobial preservative. Propylene glycol, which is generally used as a penetration enhancer and co-solvent as well as anti-freeze agent, also has preservative functions, if included at 0.1 % to 2 % concentration.

In some embodiments, the addition of a preservative is avoided by using either a single use device, or by use of a device equipped with antimicrobial material in the pump and the outlet such as silver or gold particles and air filters or silver or gold lining at the inner surfaces of the spray nozzle and the pump, to prevent bacterial contamination of the fluid reservoir, as described by Klöcker et al. [Klöcker, Norbert, et al. "Antimicrobial safety of a preservative-free nasal multiple-dose drug administration system." European journal of pharmaceutics and biopharmaceutics 57.3 (2004): 489-493].

In certain embodiments, seletracetam and pharmaceutically acceptable excipients are combined to increase the solubility and/or stability of seletracetam in aqueous media. Such excipients include but are not limited to ethanol, propylene glycol, polyethylene glycol, polysorbate 80, meglumine, and alike. In such formulations, seletracetam is contained at a concentration of about 25 mg/mL, about 30 mg/ml; about 35 mg/mL; about 40 mg/ml; about 45 mg/mL; about 50 mg/ml; about 60 mg/mL; about 70 mg/mL; about 80 mg/mL; about 90 mg/mL; about 100 mg/mL; about 150 mg/mL, about 200 mg/ml; about 225 mg/ml; about 250 mg/mL; about 275 mg/mL; about 300 mg/mL, about 350 mg/ml, about 400 mg/ml, about 450 mg/ml, about 500 mg/ml, about 600 mg/ml, about 700 mg/ml, about 800 mg/ml, about 900 mg/ml, about

1000 mg/ml, or about 1200 mg/ml. In some embodiments, the formulation comprising seletracetam is sterile.

In some embodiments, surfactants, tonicity agents, suspending agents, and mucoadhesive agents are used to prepare nasal spray or oromucosal spray suspensions or solutions. In certain embodiments, the surfactant is selected from the group consisting of: Polysorbate 80 NF, polyoxyethylene 20 sorbitan monolaurate, polyoxyethylene (4) sorbitan monolaurate, polyoxyethylene 20 sorbitan monopalmitate, polyoxyethylene 20 sorbitan monostearate, polyoxyethylene (4) sorbitan monostearate, polyoxyethylene 20 sorbitan tristearate, polyoxyethylene (5) sorbitan monooleate, polyoxyethylene 20 sorbitan trioleate, 20 polyoxyethylene 20 sorbitan monoisostearate, sorbitan monooleate, sorbitan monolaurate, sorbitan monopalmitate, sorbitan monostearate, sorbitan trilaurate, sorbitan trioleate, sorbitan tristearate, mixtures thereof, and the like. In certain embodiments, the tonicity agent is selected from the group consisting of: dextrose, lactose, sodium chloride, mixtures thereof, and the like. In some embodiments, the suspending agent is selected from the group consisting of: microcrystalline cellulose, carboxymethylcellulose sodium NF, polyacrylic acid, magnesium aluminum silicate, xanthan gum, mixtures thereof, and the like.

In some embodiments, the mucoadhesive agent is selected from the group consisting of microcrystalline cellulose, sodium carboxymethylcellulose, methyl cellulose, hydroxyethyl cellulose (e.g., Natrosol™ 250 M), hydroxypropyl cellulose, polyacrylic acid, dodecyl maltoside, sucrose dodecanoate, fish gelatin, gelatin type A, mannitol, or hyaluronic acid. In certain embodiments, the hyaluronic acid is a hyaluronic acid polymer having a molecular weight of about 3,000 Dalton, about 10,000 Dalton, about 25,000 Dalton, about 50,000 Dalton, about 100,000 Dalton, about 350,000 Dalton, about 1,000,000 Dalton, or about 3,000,000 Dalton. In some embodiments, the concentration of the mucoadhesive agent is 0.01% to 3.0% (w/w). In preferred embodiments, the mucoadhesive agent is hydroxyethyl cellulose (e.g., Natrosol™ 250 M).

In some embodiments, the formulation comprises the mucoadhesive agent at a concentration of 0.2% w/w to 10% w/w, 0.5% w/w to 5% w/w, 0.5% w/w to 2% w/w, 0.5% w/w to 1.5% w/w, about 0.75% w/w, or about 1% w/w. In preferred embodiments, the formulation comprises 0.5% w/w to 2% w/w of the mucoadhesive agent. In more preferred embodiments, the formulation comprises about 0.75% w/w of the mucoadhesive agent. In some embodiments, the

formulation comprises hydroxyethyl cellulose (e.g., Natrosol™ 250 M) at a concentration of 0.2% w/w to 10% w/w, 0.5% w/w to 5% w/w, 0.5% w/w to 2% w/w, 0.5% w/w to 1.5% w/w, about 0.75% w/w, or about 1% w/w. In preferred embodiments, the formulation comprises 0.5% w/w to 2% w/w of the hydroxyethyl cellulose. In more preferred embodiments, the formulation comprises about 0.75% w/w of the hydroxyethyl cellulose.

In certain embodiments, the formulation comprises about 0.01 % to about 0.50% (w/w), about 0.08% to about 0.40% (w/w), or about 0.10% to about 0.30% (w/w) of the antimicrobial preservative. In certain embodiments, the formulation comprises about 0.01 % to about 2.50% (w/w), about 0.03% to about 1.0% (w/w), or about 0.05% to about 0.50% (w/w) of the mucoadhesive agent. In certain embodiments, the formulation comprises about 0.001 % to about 0.050% (w/w), about 0.004% to about 0.030% (w/w), or about 0.005% to about 0.020% (w/w) of the surfactant. In some embodiments, the formulation comprises about 1.0% to about 10.0% (w/w), about 3.0% to about 7.0% (w/w), or about 4.0% to about 6.0% (w/w) of the tonicity agent. In certain embodiments, the formulation comprises about 0.5% to about 5.0% (w/w), about 1.0% to about 3.0% (w/w), or about 1.5% to about 2.0% (w/w) of the suspending agent.

In some embodiments, seletracetam dissolved in the pharmaceutically acceptable aqueous excipient solution suitable for solubilizing seletracetam at the desired concentration is adjusted to a pH between about 3-10, about 4-9, about 4-8, about 4-7, about 4-6, about 4-5, about 5-9, about 5-8, about 5-7, about 5-6, about 4.5-7.5, or about 5.5-7.5. In certain embodiments, seletracetam nasal formulations are formulated as an aqueous composition (e.g., in water or saline) with a pH of about 5 - 8.

Monolayer and Bilayer Films

In some embodiments, the films described herein are not dissimilar to the films used, for example, to make the Listerine® PocketPak® mouth fresheners. In PocketPak films the polymers used are typically polysaccharide-based or polysaccharide and glycoprotein-based gums such as pullulan, pectin, locust bean gum, xanthan gum, sodium alginate, gum Arabic, and the like. These same polymers can be used in the films described herein.

In certain embodiments, the films can include one layer, two layers, or more. If in two layers, the one adapted to adhere to mucosal tissue may be referred to as the “adhesive layer” With two layers, the outer layer can be less adhesive or non-adhesive and can provide protection

against mechanical agitation, such as agitation by a user's tongue. The components of the outer layer might be, of themselves, less dissolvable than the components of an adhesive layer. However, in the aggregate, the film shall dissolve in that it will transition to folly dissolved parts or parts that will be carried away by normal cleaning processes at the mucosal tissue in question. In forming two layers, diffusion, or the forming process itself, may provide a gradient in component amounts in the transition between the two layers. The two layers can be utilized to separate components (e.g., a seletracetam-containing layer and a buffered pH-neutralizing layer), which together enhance absorption of the seletracetam, but are otherwise incompatible in a formulation requiring long term stability (i.e., shelf life). Alternatively, the unit dosage form described herein may be a monolayer film that is a seletracetam-containing layer that is coated with or impregnated with a particulate base. The particulate base can be incorporated into the monolayer film using the methods described in PCT Publication No. W0/2009/052421, U.S. Patent Publication No. 20060210610, each of which is incorporated herein by reference. In some embodiments, the film described herein may include an effervescent particulate (i.e., a particulate carbonate base). Such effervescent films can be prepared as described in U.S. Patent Publication No. 20010006677, incorporated herein by reference.

In some embodiments, the polymers used in the films described herein may be polymers that affect the rate of hydration or mucosal adhesion properties of an adhesive layer. Such polymers can be, for example, carboxymethylcellulose, cellulose acetate, ethylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose (HPMC, such as Pharmacoat 606™, Shin-Etsu Chemical Company Ltd., Japan), nitrocellulose, polyoxyethylene/polyoxypropylene polymers, copolymers or block copolymers, polyvinylpyrrolidone polymers or derivatives, or gums. The average molecular weight of the polymer can be selected based on the swelling and dissolution profile sought. Mixtures of less soluble and/or less swellable polymers with more soluble or swellable polymers can help transition the film to a sufficiently dissolved form. For example, the film can include carbamer, polyethylene oxide, ethylcellulose, titanium oxide and colorant (such as F, D, and C blue lake colorants). In some embodiments, the film is formed using a pharmaceutically appropriate solvent such as ethanol, water, mixtures, or the like. Such solvents are typically largely evaporated away prior to use. Optionally, the films comprise a blend of more than one polymer or more than one molecular weight of a given set of polymers in order to control the rate of hydration, physical properties, and mechanical properties.

Basic Layers

In some embodiments, the multi-layered films described herein may include a film formed from a basic polymer. Polyamines which may be used in the unit dosage forms described herein include homo and copolymers of dimethylaminoethyl-acrylate, dimethylaminoethyl-methacrylate, dimethylaminopropyl-acrylate, dimethylaminpropyl-methacrylate, or other similar amino-functionalized acrylate, chitosan or partially hydrolyzed chitin in a substantially basic form, homo and co polymers of polyethyleiminc, polylysine, polyvinylimidazole, or polyvinylamine. In certain embodiments, the polyamine is Eudragit E100.

Other Components

In some embodiments, plasticizers, penetration enhancers, flavoring agents, preservatives, odorants, coloring agents, and the like can be included in the unit dosage forms described herein. Plasticizers will generally modify the feel, softness, and flexibility (in an unwetted state) of the unit dosage forms described herein. Penetration enhancers may, in some cases, act as plasticizers. Examples of plasticizers include, without limitation, glycerol, propylene glycol, fatty acid esters, such as glyceryl oleate, polyalcohols, sorbitan esters, citric acid esters, polyethylene glycol (e.g., PEG 400), polyvinyl alcohol, polyvinyl methyl ether, triacetin; mannitol, xylitol, and sorbitol. The plasticizer can be present in any suitable range, including, for example about 0.5% to 30%, 10% to 20%, or 15% to 18% by weight of the dry film.

In certain embodiments, penetration enhancers can be used to improve the permeability of the seletracetam at the mucosal membrane in the formulations described herein. One or more penetration enhancers may be used to modulate the rate of mucosal absorption of the seletracetam. In certain embodiments, the penetration enhancer comprises bile salts, such as sodium cholate, sodium glycocholate, sodium glycodcoxycholate, taurodeoxycholate, sodium deoxycholate, sodium lithocholate chenocholate, chenodeoxycholate, ursocholate, ursodeoxy-cholate, hyodeoxycholate, dehydrocholate, glycochenocholate, taurochenocholate, and taurochenodeoxycholate; sodium dodecyl sulfate (SDS), dimethyl sulfoxide (DMSO), N-lauroyl sacrcosine, sorbitan monolaurate, stearyl methacrylate, N-dodecylazacyclohcptan-2-one, N-dodecyl-2-pyrrolidinone, N-dodecyl-2-piperidinone, 2-(1-nonyl)-1,3-dioxolane, N-(2-

methoxymethyl) dodecylamine, N-dodecylethanolamine, N-dodecyl-N-(2-methoxymethyl)acetamide, 1-N-dodecyl-2-pyrrolidone-5-carboxylic acid, 2-pentyl-2-oxo-pyrrolidineacetic acid, 2-dodecyl-2-oxo-1-pyrrolidineacetic acid, 2-dodecyl-2-oxo-l-pyrrolidineacetic acid, 1-azacylioheptan-2-one-dodecylacetic acid, menthol, propylene glycol, glycerol monostearate, sorbitol monolaurate, glycerol dilaurate, tocopherol acetate, phosphatidyl choline, glycerol, polyethyleneglycol, monoglycerides, diglycerides, triglycerides, lecithin, tween surfactants, sorbitan surfactants, sodium lauryl sulfate; salts and other derivatives of saturated and unsaturated fatty acids, surfactants, bile salt analogues, derivatives of bile salts, alkyl glycosides such as tetradecyl maltoside or dodecyl maltoside (Intravail®) as described in U.S. Pat. No. US 9,283,280, or such synthetic penetration enhancers as described in U.S. Pat. No. 4,746,508, which are both incorporated herein by reference.

In some embodiments, a flavoring agent and/or odorant may be added to the unit dosage forms described herein to make them more palatable and may be added to mask an inherent taste. At least one flavoring agent or odorant composition may be used. Any effective flavor or odor may be rendered. The flavoring agents may be natural, artificial, or a mixture thereof. The flavoring agent may provide a flavor that is attractive to the user. In certain embodiments, the flavoring agent may give the flavor of mint, honey lemon, orange, lemon-lime, grape, cranberry, vanilla berry, Magnasweet™, bubble gum, or cherry. The flavoring agent may be a natural or artificial sweetener, such as sucrose, xylitol, sodium saccharin, cyclamate, aspartame, acesulfame, and salts thereof. In some embodiments, the formulation comprises a flavoring agent, wherein the flavoring agent comprises vanilla extract, cinnamon, ginger, vanillin, linalool, coumarin, or a citrus oil.

In some embodiments, to minimize the risk for oxidative degradation of seletracetam, it is desirable that the formulations described herein contain one or more antioxidants. Antioxidants that can be used in the films described herein may be selected from thiols (e.g., aurothioglucose, dihydrolipoic acid, propylthiouracil, thioredoxin, glutathione, cysteine, cystine, cystamine, thiodipropionic acid), sulphoximines (e.g., buthionine-sulphoximines, homocysteine-sulphoximine, buthionine-sulphones, and penta-, hexa- and heptathionine-sulphoximinc), metal chelators (e.g, a-hydroxy-fatty acids, palmitic acid, phytic acid, lactoferrin, citric acid, lactic acid, and malic acid, humic acid, bile acid, bile extracts, bilirubin, biliverdin, EDTA, EGTA, and DTPA), sodium metabisulfite, vitamins (e.g., vitamin E, vitamin C, ascorbyl palmitate, Mg

ascorbyl phosphate, and ascorbyl acetate), phenols (e.g., butylhydroxytoluene, butylhydroxyanisole, ubiquinol, nordihydroguaiaretic acid, trihydroxybutyrophenone), benzoates (e.g., coniferyl benzoate), uric acid, mannose, propyl gallate, selenium (e.g., selenium-methionine), stilbenes (e.g., stilbene oxide and trans-stilbene oxide), and combinations thereof. The total amount of antioxidant included in the films can be from 0.001 % to 3% by weight, preferably 0.01% to 1% by weight, in particular 0.05% to 0.5% by weight, based on the total weight of the formulation. In certain embodiments, the formulation comprises an antioxidant. In some embodiments, the antioxidant comprises ascorbic acid, sodium bisulfite, butylated hydroxytoluene, sodium metabisulfite, or tocopherol.

In certain embodiments, the various components (e.g., plasticizers, penetration enhancers, flavoring agents, preservatives, odorants, coloring agents, particulate base, and seletracetam particles, e.g. seletracetam co-crystal particles) included in the formulations described herein may be combined and incorporated into a first portion that includes the seletracetam or combined and incorporated into a second portion that is basic and includes a pH neutralizing component, or the components may be divided between the two portions. In some embodiments, it may be desirable to minimize interaction between the seletracetam-containing portion of the unit dosage form and the basic portion of the unit dosage form by including a barrier between the two. In certain embodiments, a barrier can be included in the formulations described herein as a third layer interposed between the acidic layer and the basic layer of a multilayer sublingual formulation. In some embodiments, the barrier can be a rapidly dissolving coating on the surface of a particulate component in the formulation, such as a coated particulate base coated onto, or embedded within, an acidic portion of the formulation. In some embodiments, the barrier can be a rapidly dissolving coating on the surface of seletracetam particles in the unit dosage form, which further includes a basic portion. These approaches can be utilized to ensure that the seletracetam-containing portion of the formulation is not neutralized prior to the administration to a subject.

Seletracetam Particles

In certain embodiments, seletracetam is water soluble and may be incorporated in any film-forming base as a solution. In some embodiments, seletracetam is added in particulate from. For such particulate form addition, both, seletracetam particles and seletracetam co-crystal

particles may be selected. In certain embodiments, the formulations described herein include seletracetam or seletracetam co-crystal particles having an effective particle size of about 1 micron to about 10 microns. In certain embodiments, the starting seletracetam composition can be predominantly crystalline and can include unmodified seletracetam or seletracetam co-crystals, which represent with diverse crystal forms. In some embodiments, the pharmaceutical formulations described herein can include seletracetam particles or seletracetam co-crystal particles having an effective particle size of less than about 1 micron (i.e., nanoparticulate formulations). In certain embodiments, the starting seletracetam composition can be predominantly crystalline and can include unmodified seletracetam or seletracetam co-crystals with diverse crystal forms. Seletracetam or seletracetam co-crystal particles may be made by using any method known in the art for achieving the desired particle sizes. Useful methods include, for example, milling, homogenization, supercritical fluid fracture, or precipitation techniques. Exemplary methods are described in U.S. Patent Nos. 4,540,602; 5,145,684; 5,518,187; 5,718,388; 5,862,999; 5,665,331; 5,662,883; 5,560,932;5,543,133; 5,534,270; and 5,510,118; 5,470,583, each of which is specifically incorporated by reference.

Milling To Obtain Submicron Seletracetam Particles

In some embodiments, the seletracetam or seletracetam co-crystals are milled in order to obtain micron or submicron particles. The milling process can be a dry process, e.g., a dry roller milling process, or a wet process, i.e., wet-grinding. A wet-grinding process is described in U.S. Pat. Nos. 4,540,602, 5,145,684, 6,976,647, and EP0498482, the disclosures of which are hereby incorporated by reference. Thus, the wet grinding process can be practiced in conjunction with a liquid dispersion medium and dispersing or wetting agents such as described in these publications. Useful liquid dispersion media include safflower oil, ethanol, n-butanol, hexane, or glycol, among other liquids selected from known organic pharmaceutical excipients (see U.S. Patent Nos. 4,540,602 and 5,145,684), and can be present in an amount of 2.0-70%, 3.0-50%, or 5.0-25% by weight based on the total weight of the seletracetam in the formulation.

In certain embodiments, the grinding media for the particle size reduction step can be selected from rigid media, typically spherical in shape, though non-spherical grinding media could also be used. The grinding media may have a mean particle size from 1 mm to about 500 microns. For fine grinding, the grinding media particles may have a mean particle size from

about 0.05 to about 0.6 mm. In some embodiments, smaller-size grinding media will result in smaller size seletracetam or seletracetam co-crystal particles as compared to the same conditions using larger-sized grinding media. In selecting material, grinding media with higher density, e.g., glass (2.6 g/cm^3), zirconium silicate (3.7 g/cm^2 and zirconium oxide (5.4 g/cm^3) and 95% zirconium oxide stabilized with yttrium, can be utilized for more efficient milling. In some embodiments, polymeric grinding media can be used. Polymeric resins suitable for use herein may be chemically and physically inert, substantially free of metals, solvent, and monomers, and of sufficient hardness and friability to enable them to avoid being chipped or crushed during grinding. Suitable polymeric resins include, without limitation, cross-linked polystyrenes, such as polystyrene crosslinked with divinylbenzene, styrene copolymers, polycarbonates, polyacetals, such as Delrin ™, vinyl chloride polymers and copolymers, polyurethanes, polyamides, poly(tetrafluoroethylenes), e.g., Teflon™, and other fluoropolymers, high density polyethylenes, polypropylenes, cellulose ethers and esters such as cellulose acetate, polyhydroxymethacrylate, polyhydroxyethyl acrylate, and silicone containing polymers such as polysiloxanes. Grinding can take place in any suitable grinding mill. Suitable mills include an airjet mill, a roller mill, a ball mill, an attritor mill, a vibratory mill, a planetary mill, a sand mill, and a bead mill. A high-energy media mill is preferred when small particles are desired. The mill can contain a rotating shaft.

In some embodiments, the proportions of the grinding media, seletracetam or seletracetam co-crystals, the optional liquid dispersion medium, and dispersing, wetting, or other particle stabilizing agents present in the grinding vessel can vary within wide limits and depend on, for example, the size and density of the grinding media, the type of mill selected, the time of milling, etc. The process can be carried out in a continuous, batch, or semi-batch mode. In high-energy media mills, it can be desirable to fill 80-95% of the volume of the grinding chamber with grinding media. In roller mills, it may be desirable to leave the grinding vessel up to half filled with air, the remaining volume comprising the grinding media and the liquid dispersion media, if present. This may permit a cascading effect within the vessel on the rollers which permits efficient grinding. In some embodiments, when foaming is a problem during wet grinding, the vessel can be completely filled with the liquid dispersion medium or an anti-foaming agent may be added to the liquid dispersion. The attrition time can vary widely and depends primarily upon the mechanical means and residence conditions selected, and the initial and desired final particle

size, among other factors. For roller mills, processing times from several days to weeks may be required. In some embodiments, milling residence times of less than about 2 hours are generally required using high-energy media mills. In certain embodiments, after attrition is completed, the grinding media is separated from the milled seletracetam particulate product (in either a dry or liquid dispersion form) using conventional separation techniques, such as by filtration, or sieving through a mesh screen.

In some embodiments, to produce seletracetam or seletracetam co-crystal particles having an effective particle size of less than about 1 micron, the grinding media can be made from beads having a size ranging from 0.05 mm to 4 mm. For example, high energy milling of seletracetam, with yttrium stabilized zirconium oxide 0.4 mm beads for a milling residence time of 25 minutes to 1.5 hours in recirculation mode at 1200 to 3000 RPM. In certain embodiments, high energy milling of seletracetam or seletracetam co-crystals, with 0.1 mm zirconium oxide balls for a milling residence time of 2 hours in batch mode can be used. In some embodiments, the milling concentration can be from about 10% to about 30% seletracetam by weight in comparison to the milling slurry weight, which can contain a wetting and/or dispersing agent to coat the initial suspension so a uniform feed rate may be applied in continuous milling mode.

In certain embodiments, batch milling mode is utilized with a milling media containing an agent to adjust viscosity and/or provide a wetting effect so that the seletracetam is well dispersed amongst the grinding media.

Microprecipitation To Obtain Seletracetam Nanoparticles

In some embodiments, seletracetam or seletracetam co-crystal particles may be prepared by homogeneous nucleation and precipitation in the presence of a wetting agent or dispersing agent using methods analogous to those described in U.S. Patent Nos. 5,560,932 and 5,665,331, which are specifically incorporated by reference. Such a method can include the steps of: (1) dispersing seletracetam or seletracetam co-crystals in a suitable liquid media; (2) adding the mixture from step (1) to a mixture including at least one dispersing agent or wetting agent such that at the appropriate temperature, the seletracetam is dissolved; and (3) precipitating the formulation from step (2) using an appropriate anti-solvent. The method can be followed by the removal of any formed salt, if present, by dialysis or filtration and the concentration of the dispersion by conventional means. In certain embodiments, the seletracetam particles are present

in an essentially pure form and dispersed in a suitable liquid dispersion media. In this approach, the seletracetam particles are a discrete phase within the resulting mixture. In some embodiments, useful dispersing agents, wetting agents, solvents, and anti-solvents can be experimentally determined.

Homogenization To Obtain Seletracetam Nanoparticles

In some embodiments, seletracetam or seletracetam co-crystal particles may be prepared by high-pressure homogenization (see U.S. Patent No. 5,510,118). In this approach, seletracetam or seletracetam co-crystal particles are dispersed in a liquid dispersion medium and subjected to repeated homogenization to reduce the particle size of the seletracetam particles to the desired effective average particle size. The seletracetam particles can be reduced in size in the presence of at least one or more dispersing agents or wetting agents. In certain embodiments, the seletracetam particles can be contacted with one or more dispersing agents or wetting agents either before or after attrition. Other materials, such as a diluent, can be added to the seletracetam/dispersing agent mixture before, during, or after the size reduction process. In some embodiments, unprocessed seletracetam can be added to a liquid medium in which it is essentially insoluble to form a premix (i.e., about 0.1-60% w/w seletracetam and about 20-60% w/w dispersing agents or wetting agents). The apparent viscosity of the premix suspension may be less than about 1000 centipoise. The premix can then be transferred to a microfluidizer and circulated continuously first at low pressures, and then at maximum capacity (i.e., 3,000 to 30,000 psi) until the desired particle size reduction is achieved. The resulting dispersion of seletracetam particles can be spray coated onto a sublingual pharmaceutical formulation using techniques well known in the art.

Milling With Simethicone

In some embodiments, foaming during the nanosizing can present formulation issues and can have negative consequences for particle size reduction. For example, high levels of foam or air bubbles in the mill can cause a drastic increase in viscosity rendering the milling process inoperable. Even a very low level of air presence can dramatically reduce milling efficiency making the desired particle size unachievable. This may be due to the resultant air in the mill cushioning the milling balls and limiting grinding efficiency. The air also can form a

microemulsion with the milled ingredients which presents many issues concerning the delivery of an accurate dose and palatability. In certain embodiments, the addition of a small amount of simethicone is an effective anti-foaming agent which minimizes milling variability or special handling techniques to avoid the introduction of air into the milling process.

The Use Of Wetting And Dispersing Agents

In some embodiments, the seletracetam or seletracetam co-crystal particles can be prepared with the use of one or more wetting and/or dispersing agents, which are, e.g., adsorbed on the surface of the seletracetam or seletracetam co-crystal particle. The seletracetam particles can be contacted with wetting and/or dispersing agents either before, during or after size reduction. Generally, wetting and/or dispersing agents fall into two categories: non-ionic agents and ionic agents. The most common non-ionic agents are excipients which are contained in classes known as binders, fillers, surfactants, and wetting agents. Limited examples of non-ionic surface stabilizers are hydroxypropylmethylcellulose, polyvinylpyrrolidone, Plasdone, polyvinylalcohol, Pluronics, Tweens and polyethylene glycols (PEGs). Ionic agents are typically organic molecules bearing an ionic bond such that the molecule is charged in the formulation, such as long-chain sulfonic acid salts (e.g., sodium lauryl sulfate and dioctyl sodium sulfosuccinate). Excipients, such as wetting and dispersing agents, can be applied to the surface of the seletracetam nanoparticulate via spray drying, spray granulation, or spray layering process. These procedures are well known in those skilled in the art. It is also common to add additional excipients prior to the removal of solvent in the nanoparticulate suspension to aid in the dispersion of the solid composition in the medium in which the solid composition will be exposed (e.g. saliva) to further prevent agglomeration and/or particle size growth of the small seletracetam particles. An example of such an additional excipient is a redispersing agent. Suitable redispersing agents include, without limitation, sugars, polyethylene glycols, urea and quarternary ammonium salts.

Therapy

In some aspects, the diseases and conditions treatable using the sublingual/buccal or intranasal or oromucosal formulations are as listed herein above, and include, but are not limited to, epilepsy, seizure disorders, acute repetitive seizures, pain including, but not limited to,

neuropathic pain, migraine, visceral pain, cancer break through pain, post-surgical pain, chronic pain, neuralgia, or cluster headache. In some embodiments, the sublingual/buccal formulations described herein include rapidly disintegrating or dissolving dosage forms (e.g. an orally disintegrating tablet), also known as fast dissolve, fast or rapid melt, and quick disintegrating dosage forms. In some embodiments, these dosage forms dissolve or disintegrate rapidly in the patient's mouth without chewing or the need for water within a short time frame. In some embodiments, intranasal formulations are designed to allow a rapid mucosal uptake of the dosage form, leading to rapid onset of pharmacological action. In some embodiments, the liquid formulations designed as intranasal formulations, can be also administered to the oromucosal surface and are designed to allow a rapid oromucosal uptake of the dosage form, leading to rapid onset of pharmacological action. In such instances, the spray formulations for oromucosal administration may contain in addition sweeteners, taste masing agent or flavors, to improve patient acceptance.

In certain embodiments, because of their ease of administration, such formulations are particularly useful for the specific needs of patients with severe neurological diseases including epilepsy, acute repetitive seizures, and also in patients with developmental delay or severe acquired brain injury such as head injury, stroke, or central nervous system ("CNS") infection. The sublingual/buccal formulations may be in unit dosage form in the shape of, for example, a lozenge, a pill, a tablet, a film, or a strip. In some embodiments, the sublingual/buccal formulations may be prepared in non-unit dosage forms, such as a gel. In certain embodiments, intranasal formulations are administered with a metered dose administration device (e.g. a nasal spray device). In certain embodiments, the formulation described herein includes seletracetam.

In certain embodiments, the formulations can be administered to patients in therapeutically effective amounts. In some embodiments, an amount is administered that prevents, reduces, or eliminates the symptoms of epilepsy or seizure disorder, or pain. In some embodiments, the dose range is from about 1 mg to about 600 mg of seletracetam, given as a single dose or up to five times per day. In certain embodiments, the dosage of seletracetam to be administered will depend on such variables as the type and extent of the condition, the overall health status of the particular patient, the particular form of seletracetam being administered, and the particular sublingual/buccal or intranasal formulation being used. In some embodiments, the single dose may be increased to up to 600 mg/dose (e.g., 500 mg/dose), by administering

multiple dose units simultaneously or consecutively with administration every 1-10 min per dosage unit form. In certain embodiments, for intranasal formulations, the formulation may be administered in one nostril, or sequentially in both nostrils (1 to 5 unit doses per nostril).

In some embodiments, the formulation is adapted for sublingual/buccal or oromucosal administration. The formulation may be administered in the oral cavity, in the cheek, sublingually, or on the lip mucosal (1 to 5 unit doses per administration site). In certain embodiments, the formulation is adapted for intranasal or oromucosal administration.

In some embodiments, the formulation described herein may be used for treating a seizure disorder (e.g., epilepsy). In some embodiments, the seizure disorder comprises epilepsy, a first seizure, a febrile seizure, or eclampsia. In certain embodiments, the seizure disorder comprises epilepsy. In some embodiments, the epilepsy comprises focal onset epilepsy with retained awareness, absence epilepsy, frontal lobe epilepsy, temporal lobe epilepsy, neocortical epilepsy, juvenile myoclonic epilepsy, epilepsy with aura, reflex epilepsy, catamenial epilepsy, epilepsy without aura, focal onset epilepsy without retained awareness, Lennox-Gastaut syndrome, infantile spasms, childhood absence epilepsy, Rasmussen's encephalitis, Dravet syndrome, tuberose sclerosis complex, hypothalamic hamartoma, developmental and epileptic encephalopathy, or reflex epilepsy such as photic, reading or audiogenic or sound-induced epilepsy.

In some embodiments, the formulation described herein may be used for treating acute seizures, absence seizures, myoclonic seizures, tonic seizures, clonic seizures, tonic-clonic seizures, epileptic spasms, focal seizures with and without altered awareness, or seizure clusters or status epilepticus. In some embodiments, the epilepsy is status epilepticus or myoclonic epilepsy. In certain embodiments, the seizures are subclinical or electrographic seizures.

In certain embodiments, the formulation described herein are used for treating a pain. In some embodiments, the pain comprises neuropathic pain, neuralgia, chronic pain, peripheral nerve pain, migraine, cluster headache pain, visceral pain, inflammatory pain, cancer pain, pain associated with epilepsy, phantom pain in patients with amputations, wound pain, or post-surgical pain.

In certain embodiments, the formulation described herein are used to treat a neurological or psychiatric disorder. In some embodiments, the neurological or psychiatric disorder comprises a bipolar disorder, mania, depression, anxiety, cerebral ischemia, essential tremor, neonatal

cerebral hemorrhage, amyotrophic lateral sclerosis, spasticity, Parkinson's disease, dementia, Alzheimer's disease, Mild Cognitive Impairment (MCI), Age-related Cognitive Decline (ARCD), or Age-Associated Memory Impairment (AAMI). Related treatment methods comprising administration of seletracetam are described, for example, in US Patent Application Publication No. 2024/0293363 A1, which is incorporated by reference herein.

In patients suffering from epilepsy, clusters of seizures may occur despite taking regular antiseizure medication, and patients may require rescue treatment. Some patients can predict upcoming seizures, either based on a sensation ("aura"), body part movement, cognitive or emotional changes or changes related to the activation of the autonomic nervous system preceding the convulsive seizure, or based on seizure detection mechanisms, or seizures occur following a regular schedule, such as in the case of catamenial seizures. Likewise, patients may suffer from acute pain attacks of diseases like neuropathic pain, peripheral nerve pain, migraine, cluster headache, cancer break through pain, post-surgical pain or similar pain conditions. In all these cases, a rapid onset of anti-seizure or anti-pain treatment is desirable.

Using the sublingual/buccal or intranasal formulations described herein, a subject suffering from these seizure conditions or from pain conditions may self-medicate to treat their condition, or relatives or caretakers may administer the respective dosing form as rescue treatment. The sublingual formulations are easy for a subject to administer and can relieve the seizures or can prevent the occurrence of further seizures in the case of a seizure cluster or break through pain conditions. Intranasal formulations may also be administered for the same purpose.

The sublingual/buccal, oromusosal and intranasal formulations described herein may increase the bioavailability of seletracetam and improve the safety and efficacy of anti-seizure and analgesic therapy. The formulations may produce a rapid uptake of seletracetam into the subject, allowing seizure episodes to be self-treated. Furthermore, the convenience with which these sublingual/buccal or intranasal formulations can be self-administered may be particularly desirable for severely ill patients, such as those with severe epilepsy disease with mental retardation.

In certain aspects, described herein are (i) sublingual/buccal formulations in unit dosage form comprising a first portion comprising seletracetam, and a second portion comprising a pH neutralizing agent; (ii) sublingual/buccal formulations comprising seletracetam or seletracetam

co-crystal particles having an effective particle size of from 20 nm to 10 μm; and/or (iii) sublingual/buccal formulations comprising seletracetam complexed to an anionic polyelectrolyte.

Definitions

Unless otherwise defined herein, scientific and technical terms used in this application shall have the meanings that are commonly understood by those of ordinary skill in the art. Generally, nomenclature used in connection with, and techniques of, chemistry, cell and tissue culture, molecular biology, cell and cancer biology, neurobiology, neurochemistry, virology, immunology, microbiology, pharmacology, genetics and protein and nucleic acid chemistry, described herein, are those well known and commonly used in the art.

The methods and techniques of the present disclosure are generally performed, unless otherwise indicated, according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout this specification. See, e.g. "Principles of Neural Science", McGraw-Hill Medical, New York, N.Y. (2000); Motulsky, "Intuitive Biostatistics", Oxford University Press, Inc. (1995); Lodish et al., "Molecular Cell Biology, 4th ed.", W. H. Freeman & Co., New York (2000); Griffiths et al., "Introduction to Genetic Analysis, 7th ed.", W. H. Freeman & Co., N.Y. (1999); and Gilbert et al., "Developmental Biology, 6th ed.", Sinauer Associates, Inc., Sunderland, MA (2000).

Chemistry terms used herein, unless otherwise defined herein, are used according to conventional usage in the art, as exemplified by "The McGraw-Hill Dictionary of Chemical Terms", Parker S., Ed., McGraw-Hill, San Francisco, C.A. (1985).

All of the above, and any other publications, patents and published patent applications referred to in this application are specifically incorporated by reference herein. In case of conflict, the present specification, including its specific definitions, will control.

The term "agent" is used herein to denote a chemical compound (such as an organic or inorganic compound, a mixture of chemical compounds), a biological macromolecule (such as a nucleic acid, an antibody, including parts thereof as well as humanized, chimeric and human antibodies and monoclonal antibodies, a protein or portion thereof, e.g., a peptide, a lipid, a carbohydrate), or an extract made from biological materials such as bacteria, plants, fungi, or animal (particularly mammalian) cells or tissues. Agents include, for example, agents whose structure is known, and those whose structure is not known.

A "patient," "subject," or "individual" are used interchangeably and refer to either a human or a non-human animal. These terms include mammals, such as humans, primates, livestock animals (including bovines, porcines, etc.), companion animals (e.g., canines, felines, etc.) and rodents (e.g., mice and rats).

"Treating" a condition or patient refers to taking steps to obtain beneficial or desired results, including clinical results. As used herein, and as well understood in the art, "treatment" is an approach for obtaining beneficial or desired results, including clinical results. Beneficial or desired clinical results can include, but are not limited to, alleviation or amelioration of one or more symptoms or conditions, diminishment of extent of disease, stabilized (i.e. not worsening) state of disease, preventing spread of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment. In certain embodiments, "treating" refers to terminating one or more symptoms or conditions. In some embodiments, "treating" refers to stabilizing disease progression (e.g., halting, delaying, or slowing disease progression).

The term "preventing" is art-recognized, and when used in relation to a condition, such as a local recurrence (e.g., pain), a disease such as cancer, a syndrome complex such as heart failure or any other medical condition, is well understood in the art, and includes administration of a composition which reduces the frequency of, or delays the onset of, symptoms of a medical condition in a subject relative to a subject which does not receive the composition. Thus, prevention of cancer includes, for example, reducing the number of detectable cancerous growths in a population of patients receiving a prophylactic treatment relative to an untreated control population, and/or delaying the appearance of detectable cancerous growths in a treated population versus an untreated control population, e.g., by a statistically and/or clinically significant amount.

"Administering" or "administration of" a substance, a compound or an agent to a subject can be carried out using one of a variety of methods known to those skilled in the art. For example, a compound or an agent can be administered, intravenously, arterially, intradermally, intramuscularly, intraperitoneally, subcutaneously, ocularly, sublingually, orally (by ingestion), intranasally (by inhalation, by instillation, or by spray application), intraspinally, intracerebrally, and transdermally (by absorption, e.g., through a skin duct). A compound or agent can also

appropriately be introduced by rechargeable or biodegradable polymeric devices or other devices, e.g., patches and pumps, or formulations, which provide for the extended, slow or controlled release of the compound or agent. Administering can also be performed, for example, once, a plurality of times, and/or over one or more extended periods.

Appropriate methods of administering a substance, a compound or an agent to a subject will also depend, for example, on the age and/or the physical condition of the subject and the chemical and biological properties of the compound or agent (e.g., solubility, digestibility, bioavailability, stability and toxicity). In some embodiments, a compound or an agent is administered orally, e.g., to a subject by ingestion. In some embodiments, the orally administered compound or agent is in an extended release or slow release formulation, or administered using a device for such slow or extended release.

As used herein, the phrase "conjoint administration" refers to any form of administration of two or more different therapeutic agents such that the second agent is administered while the previously administered therapeutic agent is still effective in the body (e.g., the two agents are simultaneously effective in the patient, which may include synergistic effects of the two agents). For example, the different therapeutic compounds can be administered either in the same formulation or in separate formulations, either concomitantly or sequentially. Thus, an individual who receives such treatment can benefit from a combined effect of different therapeutic agents.

A "therapeutically effective amount," "effective amount," "pharmaceutically effective amount," or a "therapeutically effective dose" of a drug or agent is an amount of a drug or an agent that, when administered to a subject will have the intended therapeutic effect. The full therapeutic effect does not necessarily occur by administration of one dose, and may occur only after administration of a series of doses. Thus, a therapeutically effective amount may be administered in one or more administrations. The precise effective amount needed for a subject will depend upon, for example, the subject's size, health and age, and the nature and extent of the condition being treated, such as cancer or MDS. The skilled worker can readily determine the effective amount for a given situation by routine experimentation.

As used herein, the term "seletracetam particles" refers to microparticles or nanoparticles containing seletracetam or any seletracetam co-crystal.

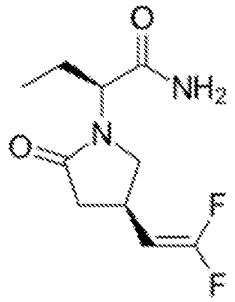
As used herein, the term "average circulating concentration" refers to the average plasma concentration of seletracetam at a time, observed for a group of subjects following sublingual, buccal, or intranasal administration of a particular unit dosage form described herein. For example, among 20 subjects the average circulating concentration of seletracetam 10 minutes following sublingual, buccal or intranasal administration of the unit dosage form can be at least 20 ng/mL, 30 ng/mL, 40 ng/mL, 50 ng/mL, 60 ng/mL, 75 ng/mL, 100 ng/mL, 250 ng/ml, 500 ng/ml, 750 ng/ml, 1000 ng/ml or 2000 ng/ml, depending upon the amount of seletracetam in the unit dosage. For high-dose administration or following sequential administration of multiple doses, the plasma concentration may reach up to 15,000 ng/ml.

The term “Pain” refers to any kind of pain, including but not limited to neuropathic pain, neuralgia, chronic pain, peripheral nerve pain, migrain, cluster headache pain, visceral pain, inflammatory pain, cancer pain including cancer break through pain, pain associated with epilepsy, phantom pain in patients with amputations, wound pain, post-surgical pain, and any other form of pain.

The term “seletracetam” refers to a chemical molecule, used as a drug. Seletracetam (UCB 44212) is a pyrrolidone-derived drug of the racetam family that is structurally related to levetiracetam (trade name Keppra). There are two main mechanisms of action for seletracetam. The first is its high-affinity stereospecific binding to synaptic vesicle glycoprotein 2A (SV2A). Seletracetam has shown potent seizure suppression in models of acquired and genetic epilepsy and has been well tolerated by various animal models. Seletracetam has shown potent anticonvulsant effects in patients suffering from seizure disorders. The second is its binding to N-type calcium channels and preventing the influx of Ca^{2+} during high-voltage activation which is typical of epilepsy. Seletracetam has also analgesic properties.

Seletracetam has shown anti-seizure activity in patients if orally administered at a typical dose range of 0.03–12 mg/kg per day. Therapeutically active plasma levels range from 10 ng to 2,000 ng/ml, but may transiently reach up to 15,000 ng/ml following high-dose administration, without inducing severe toxicity.

The chemical structure of seletracetam is presented below.



Seletracetam is compound 222 in the patent US 6806287 B2. The CAS number is 357336-83-5.

As used herein, the terms "effective particle size" and "particle size" are used interchangeably and refer to a mixture of particles having a distribution in which 50% of the particles are below and 50% of the particles are above a defined measurement. The "effective particle size" refers to the volume-weighted median diameter as measured by a laser/light scattering method or equivalent, wherein 50% of the particles, by volume, have a smaller diameter, while 50% by volume have a larger diameter. The effective particle size can be measured by conventional particle size measuring techniques well known to those skilled in the art. Such techniques include, for example, sedimentation field flow fractionation, photon correlation spectroscopy, light scattering (e.g., with a Microtrac UP A 150), laser diffraction, and disc centrifugation.

As used herein, "pH neutralizing agent" refers to any basic or acidic component present in the unit dosage forms described herein. The pH-neutralizing agents that can be used in the unit dosage forms described herein include organic bases (e.g., amines), inorganic bases (e.g., oxides, hydroxides, carbonates, or phosphates), and mixtures thereof, as well as organic acids, inorganic acids, and mixtures thereof, if pH lowering is intended. The pH neutralizing agent is typically present in an amount sufficient to produce a solution having a pH of between 5.0 and 9.1 (e.g., 7.4 and 9.1) when the unit dosage form is placed in 1 mL of unbuffered water at pH 7.

The phrase “pharmaceutically acceptable” is art-recognized. In certain embodiments, the term includes compositions, excipients, adjuvants, polymers and other materials and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

"Pharmaceutically acceptable salt" or "salt" is used herein to refer to an acid addition salt or a basic addition salt which is suitable for or compatible with the treatment of patients.

The term "pharmaceutically acceptable acid addition salt" as used herein means any non-toxic organic or inorganic salt of any base compounds represented by Formula I. Illustrative inorganic acids which form suitable salts include hydrochloric, hydrobromic, sulfuric and phosphoric acids, as well as metal salts such as sodium monohydrogen orthophosphate and potassium hydrogen sulfate. Illustrative organic acids that form suitable salts include mono-, di-, and tricarboxylic acids such as glycolic, lactic, pyruvic, malonic, succinic, glutaric, fumaric, malic, tartaric, citric, ascorbic, maleic, benzoic, phenylacetic, cinnamic and salicylic acids, as well as sulfonic acids such as p-toluene sulfonic and methanesulfonic acids. Either the mono or di-acid salts can be formed, and such salts may exist in either a hydrated, solvated or substantially anhydrous form. In general, the acid addition salts of compounds of Formula I are more soluble in water and various hydrophilic organic solvents, and generally demonstrate higher melting points in comparison to their free base forms. The selection of the appropriate salt will be known to one skilled in the art. Other non-pharmaceutically acceptable salts, e.g., oxalates, may be used, for example, in the isolation of compounds of Formula I for laboratory use, or for subsequent conversion to a pharmaceutically acceptable acid addition salt.

The term "pharmaceutically acceptable basic addition salt" as used herein means any non-toxic organic or inorganic base addition salt of any acid compounds represented by Formula I or any of their intermediates. Illustrative inorganic bases which form suitable salts include lithium, sodium, potassium, calcium, magnesium, or barium hydroxide. Illustrative organic bases which form suitable salts include aliphatic, alicyclic, or aromatic organic amines such as methylamine, trimethylamine and picoline or ammonia. The selection of the appropriate salt will be known to a person skilled in the art.

The term "pharmaceutically acceptable co-crystal" or "co-crystal" as used herein means any non-toxic organic or inorganic crystal structure formed by co-crystallization of seletracetam with a co-crystal forming agent, including halides and organic co-crystals.

The term "seizure disorder" as used herein refers to a seizure, a condition in which a seizure is a known symptom, or a condition that increases the risk of a seizure. In certain embodiments, the term "seizure disorder" refers to epilepsy.

The term "aura" as used herein refers to a sensation that warns the subject of an impending seizure.

The term "prodrome" as used herein refers to an early clinical manifestation of a seizure, such as depression, headache, or malaise. A prodrome may even be accompanied with local muscle fasciculations or focal seizure like activity without loss of consciousness, sometimes also named focal onset seizures. In certain embodiments, the prodrome lasts at least 5 min, at least 15 min, at least 30 min, at least 1 hour, at least 2 hours, at least 5 hours, at least 10 hours, at least 1 day, or at least 2 days. In some embodiments, the prodrome lasts from 5 min to 1 week, from 5 min to 2 days, from 5 min to 1 day, from 5 min to 10 hours, from 5 min to 5 hours, from 5 min to 2 hours, from 5 min to 1 hour, from 5 min to 30 min, from 1 hour to 1 week, from 1 hour to 2 days, from 1 hour to 1 day, from 1 hour to 10 hours, from 1 hour to 5 hours, from 1 hour to 2 hours, from 2 hours to 1 week, from 2 hours to 2 days, from 2 hours to 1 day, from 2 hours to 10 hours, from 2 hours to 5 hours, from 5 hours to 1 week, from 5 hours to 2 days, from 5 hours to 1 day, from 5 hours to 10 hours, from 10 hours to 1 week, from 10 hours to 2 days, from 10 hours to 1 day, from 1 day to 1 week, from 1 day to 2 days, or from 2 days to 1 week.

The phrase "pharmaceutically acceptable carrier" as used herein means a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filter, diluent, excipient, solvent or encapsulating material useful for formulating a drug for medicinal or therapeutic use.

EXAMPLES

The invention now being generally described, it will be more readily understood by reference to the following examples, which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and are not intended to limit the invention.

Example 1: Sublingual or buccal orally disintegrating tablet of seletracetam for rapid absorption

For sublingual or buccal administration, an orally disintegrating tablet which may also contain mucoadhesive and penetration-enhancing excipients is suitable. An orally disintegrating tablet may be generated by lyophilization of a gel where seletracetam is dispersed as solution/suspension. Seletracetam has a moderate to high water solubility, i.e. in an aqueous environment, a large fraction is dissolved, while the remaining material must be finely dispersed.

To enhance the dispersion and later the rapid dissolution, micronization of the drug substance is helpful, resulting in an effective particle size of 20 nm to 10 μm.

In such a case, a self-assembling hydrogel can be formed by adding sucrose mono- or distearates at a concentration of 1% to 30% w/w, for example CRODESTA F-110 (α-D-Glucopyranoside-β-D-fructofuranosyl Octadecanoate) in a suitable buffer, which is vortexed and heated to 45 degrees for 1 hr. Then seletracetam in a fine particle or micronized form is added to the warm liquid to achieve a concentration in Suspension of 50 mg/mL (10-250 mg/ml) which is again mixed by vortexing until the solid is uniformly dissolved, suspended, and dispersed. Upon cooling to room temperature, a stable thixotropic hydrogel forms which is capable of being dispensed but which maintains the uniform suspension. Acetate buffer in the pH range of pH 2 to pH 7 is found to be particularly well suited for this purpose, but phosphate buffer at a pH range of pH 5 to pH 9 is also well suited, as is citrate buffer.

Secondary components such as preservatives, antioxidants, surfactants, viscosity enhancers, coloring agents, flavoring agents, sweeteners, mucoadhesive agents, or taste-masking agents may also be incorporated into the composition. Suitable coloring agents may include red, black and yellow iron oxides and FD&C dyes such as FD& C blue No. 2 and FD & Cred No. 40 available from Ellis & Everard. Suitable flavoring agents may include mint, raspberry, licorice, orange, lemon, grapefruit, caramel, Vanilla, cherry and grape flavors and combinations of these. Suitable sweeteners include sucrose, high fructose corn syrup, aspartame, acesulfame K, thaumatin, or stevia. Suitable taste-masking agents include sodium chloride, citric acid, or sodium bicarbonate. Suitable thickening and mucoadhesive agents include cellulose derivatives such as hydroxyethyl cellulose or hydroxypropyl cellulose, dodecyl maltoside, sucrose dodecanoate, fish gelatin, gelatin type A, or mannitol, among other agents.

Aliquots of 0.5 ml or 1 mL of the gel suspension of seletracetam are placed in the wells of a 24-well disposable microwell plastic plate and lyophilized. For lyophilization, the micro well plate containing the liquid aliquots is frozen at -70°. The frozen plate is placed within a glass lyophilization flask attached to a desktop freeze drier and lyophilized under a vacuum. Following lyophilization, the rapidly dispersing tablets are stored in the microwell plate in a dry environment until tested.

Administration of the orally disintegrating tablet upon presentation to buccal or sublingual tissue results in a rapid dissolution and uptake in the bloodstream. Within 10-15 min

after administration, therapeutic plasma levels are reached. The dose range per dosing formulation is 1 mg to 250 mg per orally disintegrating tablet. Following administration of a 30 mg dispersible tablet, a plasma level of 150 ng/ml or more is reached within 10-15 min, which is more than double as fast as compared to oral administration of the same dose. Additionally, the time to maximum drug levels is dramatically reduced, typically from one to six hours, to as little as approximately 15 to 45 minutes. Following oral administration under fasted conditions, peak plasma levels are reached within one hour, while under fed conditions, the peak plasma level is on average only reached after 2-6 h. For the treatment of patients with ongoing episodes of repetitive seizures, or for any other type of "rescue treatment", this more rapid absorption of drug, resulting in a more rapid onset of action, may be of great benefit.

Example 2: Sublingual or buccal drug-containing films containing seletracetam for rapid oromucosal absorption

Ethylcellulose, poly (ethylene oxide), and hydroxypropylcellulose are dissolved in a sufficient amount of anhydrous ethanol to form a viscous solution. The solution can contain 0.1% w/w to 20% of each of the three polymers, or may only contain a selection of two polymers at 1.0-40% total polymer concentration, combining the strip-forming properties with mucoadhesive properties of the cellulose derivatives. Microparticulate seletracetam is prepared by milling solid seletracetam using standard micronization techniques. The particulate seletracetam is suspended in the solution. As seletracetam has a moderate solubility in ethanol, part of the drug substance will be also dissolved. To ensure rapid dissolution and homogenous distribution of the remaining particles in the viscous solution, micronized material is used. After mixing and homogenization, a solvent-cast mucoadhesive film is prepared by casting a thin film of the mixture onto a sheet. Evaporation of the solvent (ethanol) can be accomplished by drying at 60 °C for 30 minutes. The resultant dry film includes a single adhesive layer that can release seletracetam if administered sublingual or to the buccal mucosa. Seletracetam can penetrate the mucosal tissue, thus enhancing the bioavailability of the drug. The single-layer film is cut into strips, each strip containing 1 mg to 250 mg of seletracetam. The strips can be administered to a subject for the treatment of seizures or related conditions.

The films described herein are not dissimilar to the films used, for example, to make the Listerine® PocketPak® mouth fresheners. In PocketPak films the polymers used may comprise polysaccharide-based or polysaccharide and glycoprotein-based gums such as pullulan, pectin,

locust bean gum, xanthan gum, sodium alginate, gum Arabic, and the like. These same polymers can be used in the films described herein. The films may comprise one layer, two layers, or more. If in two layers, the one adapted to adhere to mucosal tissue may be referred to as the "adhesive layer." With two layers, the outer layer can be less adhesive or non-adhesive, and can provide protection against mechanical agitation, such as agitation by a user's tongue. The components of the outer layer might be, of themselves, less dissolvable than the components of an adhesive layer. However, in the aggregate, the film shall dissolve in that it will transition to fully dissolved parts or parts that will be carried away by normal cleaning processes at the mucosal tissue in question. In forming two layers, diffusion or the forming process itself may provide a gradient in component amounts in the transition between the two layers. The two layers can be utilized to separate components (e.g., a seletracetam-containing layer and a dissolution-enhancing layer), which together enhance absorption of the seletracetam, but are otherwise incompatible in a formulation requiring long-term stability (i.e., shelf life). Alternatively, the film described herein may be a monolayer film that is a seletracetam-containing layer which may or may not be coated with or impregnated with a protective or mucoadhesive layer. Such effervescent films can be prepared as described in U.S. Patent Publication No. 20010006677, incorporated herein by reference.

The polymers used in the films described herein may be polymers that affect the rate of hydration or mucosal adhesion properties of an adhesive layer. Such polymers can be, for example, carboxymethylcellulose, cellulose acetate, ethylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose (HPMC), nitrocellulose, polyoxyethylene/polyoxypropylene polymers, copolymers or block copolymers, polyvinylpyrrolidone polymers or derivatives, or gums. The average molecular weight of the polymer can be selected based on the swelling and dissolution profile sought. Mixtures of less soluble and/or less swellable polymers with more soluble or swellable polymers can help transition the film to a sufficiently dissolved form. For example, the film can include carbamer, polyethylene oxide, ethylcellulose, titanium oxide and colorants (such as F, D and C blue lake colorants). The film may be formed using a pharmaceutically appropriate solvent such as ethanol, water, mixtures, or the like. Such solvents are typically largely evaporated away prior to use. Optionally, the films comprise a blend of more than one polymers, or more than one molecular weight of a given set of polymers in order to control the rate of hydration, physical properties, and mechanical properties.

The multi-layered films may include a film formed from a basic polymer. Polyamines which can be used in the film include homo and copolymers of dimethylaminoethyl-acrylate, dimethylaminoethyl-methacrylate, dimethylaminopropyl-acrylate, dimethylaminpropyl-methacrylate, or other similar amino-functionalized acrylate, chitosan or partially hydrolyzed chitin in a substantially basic form, homo and co polymers of polyethyleiminc, polylysine, polyvinylimidazole, or polyvinylamine. The polyamine may be Eudragit E100.

Example 3: Solubility Studies of Seletracetam

Solubility in water for injection

250 mg seletracetam was weighed and 200 µL water for injection was added. The majority of seletracetam powder rapidly dissolved. A small fraction of the crystalline material did not dissolve immediately. After prolonged shaking for 10 min and heating to 35°C, the remaining material was completely dissolved, resulting in a slightly yellowish liquid. The pH of this solution, representing the limit of solubility of about 1,250 mg/ml, was found to be in the range pf pH 4 to 5.

Upon cooling to refrigerated temperature for 24 h, slight precipitation was observed. An additional 50 µL of water was then added, and the solution was allowed to reach room temperature under stirring, resulting in a completely clear solution with all remaining material re-dissolved. The pH of the solution was found to be slightly acidic (i.e., 4–5) by pH paper.

Seletracetam is thus readily soluble in purified water with a maximal concentration of about 1,200 mg/mL.

Solubility in 0.9% saline

200 mg of seletracetam was weighed and 200 mL of 0.9% saline was added. The seletracetam dissolved completely after approximately 3 minutes of gentle shaking. The resulting solution was clear with a slightly yellowish color and showed no signs of precipitation after 24 hours of storage at both room temperature (20-24°C) and refrigerated temperature (2-8°C). The pH of the solution was slightly acidic, as determined using pH paper (pH 4-5).Solubility in Exploratory Intranasal or Oromucosal Spray Formulations

The solubility of seletracetam in a solution containing mucoadhesive agents and penetration enhancers was evaluated. An aqueous formulation was prepared with 0.2% hydroxyethyl cellulose as a mucoadhesive agent, 0.2% glycerin as a humectant, and 0.1% propylene glycol as a penetration enhancer, using water for injection as aqueous vehicle.

Initially, 400 mg of seletracetam was dissolved in 1 mL of this solution. However, the solution was too viscous to be effectively sprayed using a nasal spray bottle. The solution was diluted with 1 mL of water for injection, resulting in a final concentration of 200 mg/mL, which allowed the solution to be adequately sprayed with the nasal spray bottle. This solution generated an acceptable nebulization pattern, as visually inspected (droplet size and viscosity was not determined at this stage). Olfactory examination of the solution revealed no aversive smell or bitter taste.

Further formulations of 200 mg/mL seletracetam were prepared by reducing the excipients to only the mucoadhesive agent and phosphate-buffered saline (pH 7.4) as the aqueous solvent. The formulations were as follows:

Formulation A: Phosphate-buffered saline without any mucoadhesive/thickening agent.

Formulation B: 1% microcrystalline cellulose and sodium carboxymethyl-cellulose (1:1).

Formulation C: 2% microcrystalline cellulose and sodium carboxymethyl-cellulose (1:1).

Formulation D: 0.1% hydroxypropyl methylcellulose (HPMC).

Formulation E: 0.2% HPMC.

The spray quality of each formulation was visually evaluated by comparing the visible spray pattern. A wide spray angle was considered an excellent spray pattern, while a narrowed spray angle indicated less effective dispersion.

Formulation	Mucoadhesive Agent	Viscosity (cp)	Spray Pattern
A	None	1.3	Excellent
B	1% microcrystalline cellulose and sodium carboxymethyl-cellulose (1:1)	4.5	Excellent
C	2% microcrystalline cellulose and sodium carboxymethyl-cellulose (1:1)	21.8	Excellent
D	0.1% HPMC	2.8	Good

E	0.2% HPMC	4.8	Acceptable

The experiments were repeated with 100 mg/mL, 400 mg/mL and 600 mg/mL of seletracetam. The seletracetam concentration had little if any effect on the spray pattern observed.

Example 4: Intranasal or Oromucosal Solutions for Seletracetam Administration

A solution of seletracetam for intranasal administration is prepared using an aqueous buffered solution. The buffer is a phosphate buffer, which could include sodium dihydrogen phosphate, disodium hydrogen phosphate, potassium dihydrogen phosphate, dipotassium hydrogen phosphate, or alike. Alternatively, acetate buffer, citric acid buffer, or sodium citrate could be used. The solution may also include 0.3% to 0.9% sodium chloride (e.g., 0.9% sodium chloride), although due to the high concentration of seletracetam, the need for additional salt to increase osmolarity will be minimal. For concentrations of 100 mg/mL and higher, tonicity will be achieved without the addition of salt.

Nasal or oromucosal spray solutions having a seletracetam concentration of 100 mg/mL, 200 mg/mL, and 400 mg/mL are prepared by dissolving 1,000 mg, 2,000 mg, or 4,000 mg respectively of seletracetam in 10 mL of aqueous sodium dihydrogen phosphate buffered solution, using water for injection as the aqueous component. Alternatively, a low concentration sodium chloride solution, such as 0.3% or 0.5% sodium chloride, could be used. The mixture is agitated or sonicated to ensure full dissolution, which could be accelerated by applying heat up to 50°C, although dissolution is achievable at room temperature. The pH is checked and adjusted to a range of 6.0-7.5 using a dilute acid or base (e.g., hydrochloric acid or sodium hydroxide) as appropriate. The resulting solution is then sterile filtered using a 0.2-micron filter or autoclaved, and subsequently filled into glass or plastic bottles equipped with a metered dose spray top to administer approximately 50, 75, 100, 160, or 200 µL per spray actuation.

Other components which may be added to the solution include:

a) An antimicrobial preservative such as benzalkonium chloride, methylparaben, sodium benzoate, benzoic acid, phenyl ethyl alcohol, EDTA or alike at a concentration of about 0.01 % to about 0.50% (w/w);

b) A mucoadhesive/thickening agent such as tetradecylmaltoside or hydroxypropylcellulose or alike at a concentration of 0.05% to 3.0% (w/w);

c) A small quantity of antioxidants (e.g. sodium bisulfite, butylated hydroxytoluene, sodium metabisulfite, and tocopherol);
d) A humectant (e.g. glycerin, sorbitol, dexpanthenol, or mannitol);
e) A surfactant (e.g. polysorbate);
f) A mucoadhesive agent;
g) A penetration enhancer (e.g. dodecyl maltoside or tetradecyl maltoside); and
h) Other pharmaceutically acceptable excipients (e.g. tonicity agents, electrolytes, flavoring agents, and/or taste-masking agents).

Example 5: Intranasal Solutions of Seletracetam Containing Hydroxyethyl Cellulose

Three intranasal formulations of seletracetam were prepared with varying amounts of Natrosol™ 250 M—a commercially available hydroxyethyl cellulose (a mucoadhesive agent and thickening agent).

Formulation A was prepared by dissolving 2 g of Natrosol™ 250 M in 100 ml of water for injection, resulting in a 2% solution. This solution was then diluted to achieve a final concentration of 0.2% Natrosol™ 250 M by mixing 10 g of the 2% solution with 89.7 g of water for injection and 0.3 g of potassium dihydrogen phosphate. The mixture was stirred until all components were fully dissolved, resulting in a clear, viscous solution. The vehicle formulation was then sterile filtered using a 0.22 μm pore size filter. To prepare the nasal spray solution, seletracetam was added to the vehicle solution to achieve concentrations of 50, 100, 200, 400, 500, or 600 mg/mL. The mixture was agitated to ensure complete dissolution, and the pH was adjusted to 6.0-7.5 using a small quantity of 0.1% NaOH. Using a syringe equipped with a sterile filter (0.22 μm), the solution was transferred to a glass bottle equipped with a nasal spray top. After priming the pump to ensure complete filling of the pump reservoir, the spray characteristics were visually checked. Despite the addition of the mucoadhesive agent, the solution could be easily sprayed with a wide spray cone, indistinguishable from a spray cone obtained with water in the same device. The mucoadhesive properties were evaluated by spraying the fluid on a vertical surface and observing the droplets. The 0.2% solution showed prolonged residence time compared to plain water, although droplets eventually flowed down the surface.

Formulation B, which included a final concentration of 0.5% Natrosol™ 250 M, was prepared similarly to Formulation A. 25 g of the 2% Natrosol™ 250 M solution was mixed with

74.7 g of water for injection and 0.3 g of potassium dihydrogen phosphate. The resulting solution was sterile filtered and used to prepare nasal spray solutions with seletracetam concentrations of 50, 100, 200, 400, 500, or 600 mg/mL. The spray characteristics and mucoadhesive properties were evaluated similarly. The 0.5% solution maintained a wide spray cone and showed a further prolonged residence time on the vertical surface, with only a few large droplets flowing down after 2-5 minutes.

Formulation C, which included a final concentration of a 1% Natrosol™ 250 M solution, was prepared in a similar manner to Formulation A and Formulation B. 50 g of the 2% Natrosol™ 250 M solution was mixed with 49.7 g of water for injection and 0.3 g of potassium dihydrogen phosphate. The solution was sterile filtered and used to prepare nasal spray solutions with seletracetam concentrations of 50, 100, 200, 400, 500, or 600 mg/mL. The spray characteristics and mucoadhesive properties were evaluated as before. The 1% solution could still be easily sprayed, although the spray cone was slightly narrower. The residence time of droplets on the vertical surface was further prolonged, with no droplets flowing down within 5 minutes, indicating complete adhesion to the surface.

Formulation D, which included a final concentration of a 0.75% Natrosol™ 250 M solution, was prepared in a similar manner to Formulations A to C. 37.5 g of the 2% Natrosol™ 250 M solution was mixed with 62.2 g of water for injection and 0.3 g of potassium dihydrogen phosphate. The solution was sterile filtered and used to prepare nasal spray solutions with seletracetam concentrations of 50, 100, 200, 400, 500, or 600 mg/mL. The spray characteristics and mucoadhesive properties were evaluated as before. The 0.75% solution could still be easily sprayed, with a good spray cone. Thus, this Natrosol™ concentration represents a suitable concentration to maintain the spray cone. The residence time of droplets on the vertical surface was prolonged, with no droplets flowing down within 3 minutes, indicating sufficient adhesion to the surface.

Example 6: Evaluation of the Pharmacokinetics of Intranasal Seletracetam in Dogs and Humans

2 mL of Formulation C (see Example 5, above) is filled into a nasal spray bottle equipped with a spray top that administers a metered dose of approximately 100 µL. The pump is primed three times to ensure complete filling of the pump reservoir.

Dogs weighing approximately 15 kg receive one metered dose of 100 µL of the intranasal solution, prepared at a concentration of 100 mg/ml, equivalent to one spray actuation per nostril. Blood samples are collected at the following time points: 5 minutes, 10 minutes, 20 minutes, 30 minutes, and 60 minutes post-administration. Plasma is separated from the blood samples and frozen for subsequent analysis. Using a validated High-Performance Liquid Chromatography (HPLC) method, the samples are analyzed for the content of seletracetam.

The results are as follows:

after 5 minutes, plasma concentrations of seletracetam reach over 300 ng/mL;

after 10 minutes, the peak concentration exceeds 500 ng/mL; and

by 20 minutes, a decline in plasma levels is observed, with concentrations still above 400 ng/mL.

Extrapolating these data to humans, it is predicted that a dose of 30-40 mg of seletracetam, achieved by one spray per nostril of about 100 µL of a nasal spray solution with a concentration of 150 to 250 mg/mL, will result in plasma or serum concentrations exceeding 100 ng/mL within less than 5 minutes. The peak concentration is expected to be reached within approximately 10 minutes, with a rapid decline in plasma concentration thereafter, indicating that most of the drug will be fully absorbed within less than 20 minutes following intranasal administration.

In support of this extrapolation, Formulation C, prepared at a concentration of 200 mg/ml (see Example 5, above) is administered to male adult humans. The dose selected is 200 µl, i.e. one spray actuation per nostril, resulting in a total dose of about 40 mg. After 5 minutes, plasma concentrations of seletracetam reach over 400 ng/mL; after 10 minutes, the peak concentration exceeds 550 ng/mL; and by 30 minutes, a decline in plasma levels begins, with concentrations still above 500 ng/mL. At 4 h, the plasma level reaches about 250 ng/ml, i.e. still well within the therapeutic range.

Additional Administration Route

The same solution is administered by spraying it directly into the mouth of the dog. Due to the low volume of administration, the fluid is not swallowed but remains on the mucosal surface, allowing for rapid absorption.

INCORPORATION BY REFERENCE

All publications and patents mentioned herein are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

EQUIVALENTS

While specific embodiments of the subject invention have been discussed, the above specification is illustrative and not restrictive. Many variations of the invention will become apparent to those skilled in the art upon review of this specification and the claims below. The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

We claim:

1. A method of treating a seizure disorder in a subject in need thereof comprising administering seletracetam to the subject intranasally, buccally, or sublingually.

2. The method of claim 1, wherein the seizure disorder comprises epilepsy, a first seizure, a febrile seizure, or eclampsia.

3. The method of claim 1 or claim 2, wherein the seizure disorder comprises epilepsy.

4. The method of claim 3, wherein the epilepsy comprises focal onset epilepsy with retained awareness, epilepsy with aura, reflex epilepsy, catamenial epilepsy, absence epilepsy, frontal lobe epilepsy, temporal lobe epilepsy, neocortical epilepsy, juvenile myoclonic epilepsy, epilepsy without aura, focal onset epilepsy without retained awareness, Lennox-Gastaut syndrome, infantile spasms, childhood absence epilepsy, Rasmussen's encephalitis, Dravet syndrome, tuberose sclerosis complex, hypothalamic hamartoma, or developmental and epileptic encephalopathy.

5. The method of claim 4, wherein the epilepsy comprises focal onset epilepsy with retained awareness.

6. The method of claim 4, wherein the epilepsy comprises reflex epilepsy.

7. The method of claim 6, wherein the reflex epilepsy comprises photic epilepsy, reading epilepsy, or audiogenic epilepsy.

8. The method of claim 1, wherein the subject is experiencing a seizure, a seizure cluster, an aura, or a prodrome.

9. The method claim 8, wherein the subject is experiencing a seizure.

10. The method of claim 9, wherein the seizure is a focal onset seizure with retained awareness, a seizure with aura or prodrome, a reflex seizure, a catamenial seizure, an acute seizure, a secondarily generalized seizure with focal onset, an absence seizure, a myoclonic seizure, a tonic seizure, an atonic seizure, a clonic seizure, a tonic-clonic seizure, an epileptic spasm, a focal seizure, a focal onset seizure without retained awareness, a status epilepticus, a subclinical seizure, or an electrographic seizure.

11. The method of claim 9, wherein the seizure is triggered by sleep deprivation, stress, hormone changes during the menstrual cycle, drug use, drug withdrawal, a febrile illness, or a missed or incorrect dosage of chronic antiseizure medication.

12. The method of claim 10, wherein the seizure is a focal onset seizure with retained awareness.

13. The method of claim 10, wherein the seizure is a reflex seizure.

14. The method of claim 13, wherein the reflex seizure is triggered by light, sound, or reading.

15. The method of claim 8, wherein the subject is experiencing a seizure cluster or an aura.

16. The method of claim 1, wherein the subject identifies that they are experiencing a seizure, a seizure cluster, an aura, or a prodrome; and the subject administers the seletracetam within 5 minutes of the identification.

17. The method of claim 1, wherein the subject is sleep deprived, is experiencing stress, is experiencing hormone changes during their menstrual cycle, has taken a recreational drug, is experiencing drug withdrawal, is experiencing a febrile illness, or has missed or taken an incorrect dosage of their chronic antiseizure medication.

18. A method of stabilizing the progression of a focal onset seizure with retained awareness in a subject in need thereof comprising administering seletracetam to the subject intranasally, buccally, or sublingually.

19. A method of terminating a seizure in a subject in need thereof comprising administering seletracetam to the subject intranasally, buccally, or sublingually

20. A method of administering seletracetam to a subject comprising administering seletracetam to the subject intranasally, buccally, or sublingually.

21. A method of treating a pain in a subject in need thereof comprising administering seletracetam to the subject intranasally, buccally, or sublingually.

22. The method of claim 21, wherein the pain comprises neuropathic pain, peripheral nerve pain, migraine, visceral pain, cancer break through pain, post-surgical pain, chronic pain, neuralgia, or cluster headache.

23. A method of treating a neurological or psychiatric disorder in a subject in need thereof comprising administering seletracetam to the subject intranasally, buccally, or sublingually.

24. The method of claim 23, wherein the neurological or psychiatric disorder comprises bipolar disorder, mania, depression, anxiety, cerebral ischemia, essential tremor, neonatal cerebral hemorrhage, amyotrophic lateral sclerosis, spasticity, Parkinson's disease, dementia, Alzheimer's disease, Mild Cognitive Impairment (MCI), Age-related Cognitive Decline (ARCD), or Age-Associated Memory Impairment (AAMI).

25. The method of any one of claims 1–24, wherein the seletracetam is administered intranasally.

26. The method of any one of claims 1–24, wherein the seletracetam is administered buccally or sublingually.

27. The method of claim 26, wherein the seletracetam is administered buccally.

28. The method of claim 26, wherein the seletracetam is administered sublingually.

29. The method of any one of claims 1-28, comprising administering 10 mg to 80 mg of the seletracetam.

30. The method of any one of claims 1–29, wherein the method provides therapeutic plasma levels of seletracetam within 30 minutes of the administering.

31. The method of any one of claims 1–30, wherein the method provides at least 50 ng/ml seletracetam in the subject's plasma within 15 minutes of the administering.

32. The method of any one of claims 1–30, wherein the method provides at least 50 ng/ml seletracetam in the subject's plasma within 5 minutes of the administering.

33. The method of any one of claims 1–30, wherein the method provides at least 100 ng/ml seletracetam in the subject's plasma within 15 minutes of the administering.

34. The method of any one of claims 1–30, wherein the method provides at least 100 ng/ml seletracetam in the subject's plasma within 5 minutes of the administering.

35. The method of any one of claims 1–34, wherein the method provides a first-pass effect of less than 40% compared to oral administration.

36. The method of any one of claims 1-34, wherein the seletracetam is in the form of a pharmaceutically acceptable co-crystal.

37. A pharmaceutical formulation comprising seletracetam and a pharmaceutically acceptable liquid carrier.

38. The formulation of claim 37, wherein the formulation is a solution.

39. The formulation of claim 37 or claim 38, comprising 50 mg/mL to 600 mg/mL of the seletracetam.

40. The formulation of claim 39, comprising the seletracetam at a concentration of about 100 mg/mL, about 150 mg/mL, about 200 mg/mL, or about 250 mg/mL.

41. The formulation of any one of claims 37-40, further comprising a mucoadhesive agent.

42. The formulation of claim 41, comprising from 0.5% w/w to 2.0% w/w of the mucoadhesive agent.

43. The formulation of claim 41 or claim 42, wherein the mucoadhesive agent comprises hydroxyethyl cellulose, hydroxypropyl cellulose, dodecyl maltoside, sucrose dodecanoate, fish gelatin, gelatin type A, hyaluronic acid, or mannitol.

44. The formulation of claim 43, wherein the mucoadhesive agent comprises hydroxyethyl cellulose.

45. The formulation of claim 44, wherein the formulation comprises about 0.75% w/w hydroxyethyl cellulose.

46. The formulation of any one of claims 37–45, further comprising a buffering agent.

47. The formulation of claim 46, wherein the buffering agent comprises hydrochloric acid, acetic acid, citric acid, sodium hydroxide, sodium citrate, sodium carbonate, sodium tetraborate,

sodium phosphate, sodium acetate, sodium bicarbonate, potassium hydrogen phosphate, or potassium phosphate.

48. The formulation of any one of claims 37–47, further comprising a preservative.

49. The formulation of claim 48, wherein the preservative comprises sodium bisulfite, edetate disodium, sodium bisulfate, sodium thiosulfate, benzalkonium chloride, benzethonium chloride, chlorobutanol, thimerosal, phenylmercuric acetate, benzyl alcohol, phenylcarbinol, phenylmercuric nitrate, methylparaben, propylparaben, polyvinyl alcohol, phenylethyl alcohol, sodium benzoate, benzoic acid, phenyl ethyl alcohol, or ethylenediaminetetraacetic acid (EDTA)

50. The formulation of claim 48 or claim 49, wherein the concentration of the preservative in the formulation is about 0.01% to about 0.50% (w/w).

51. The formulation of any one of claims 37–50, further comprising a flavoring agent, a sweetener, an odorant, or a taste-masking agent.

52. The formulation of claim 51, wherein the formulation comprises a flavoring agent, wherein the flavoring agent comprises vanilla extract, cinnamon, ginger, vanillin, linalool, coumarin, or a citrus oil.

53. The formulation of claim 51 or claim 52, wherein the formulation comprises a sweetener, wherein the sweetener comprises sucrose, xylitol, sodium saccharin, cyclamate, high fructose corn syrup, aspartame, acesulfame K, thaumatin, or stevia.

54. The formulation of any one of claims 51–53, wherein the formulation comprises a taste-masking agent, wherein the taste-masking agent comprises sodium chloride, citric acid, or sodium bicarbonate.

55. The formulation of any one of claims 37–54, further comprising a thickening agent.

56. The formulation of claim 55, wherein the thickening agent comprises methylcellulose, ethyl cellulose, microcrystalline cellulose, hydroxypropyl methylcellulose, hydroxyethylcellulose, sodium carboxymethylcellulose, polyvinyl pyrrolidone, polyvinyl alcohol, sodium chondroitin sulfate, sodium hyaluronate, chitosan, tetradecylmaltoside, hydroxypropylcellulose, or hyaluronic acid.

57. The formulation of claim 55 or claim 56, wherein the concentration of the thickening agent is 0.05% to 3.0% (w/w).

58. The formulation of any one of claims 37–57, further comprising an antioxidant.

59. The formulation of claim 58, wherein the antioxidant comprises ascorbic acid, sodium bisulfite, butylated hydroxytoluene, sodium metabisulfite, or tocopherol.

60. The formulation of any one of claims 37–59, further comprising a humectant.

61. The formulation of claim 60, wherein the humectant comprises glycerin, sorbitol, dexpanthenol, or mannitol.

62. The formulation of any one of claims 37–61, further comprising a surfactant.

63. The formulation of claim 62, wherein the surfactant comprises dodecyl maltoside, tetradecyl maltoside, sucrose dodecanoate, sucrose mono-stearate, sucrose di-stearate, polysorbate, polysorbate 80, polysorbate 20, a polyethylene glycol ester, a polyethylene glycol, a glycerol ether, a glyceryl monoleate, lecithin, polysorbate 80 NF, polyoxyethylene 20 sorbitan monolaurate, polyoxyethylene (4) sorbitan monolaurate, polyoxyethylene 20 sorbitan monopalmitate, polyoxyethylene 20 sorbitan monostearate, polyoxyethylene (4) sorbitan monostearate, polyoxyethylene 20 sorbitan tristearate, polyoxyethylene (5) sorbitan monooleate, polyoxyethylene 20 sorbitan trioleate, 20 polyoxyethylene 20 sorbitan monoisostearate, sorbitan monooleate, sorbitan monolaurate, sorbitan monopalmitate, sorbitan monostearate, sorbitan trilaurate, sorbitan trioleate, or sorbitan tristearate.

64. The formulation of any one of claims 37–63, further comprising a penetration enhancer.

65. The formulation of claim 64, wherein the penetration enhancer comprises dodecyl maltoside, tetradecyl maltoside, a bile salt, sodium dodecyl sulfate (SDS), dimethyl sulfoxide (DMSO), N-lauroyl sacrcosine, sorbitan monolaurate, stearyl methacrylate, N-dodecylazacyclohcptan-2-one, N-dodecyl-2-pyrrolidinone, N-dodecyl-2-piperidinone, 2-(1-nonyl)-1,3-dioxolane, N-(2-methoxymethyl) dodecylamine, N-dodecylethanolamine, N-dodecyl-N-(2-methoxymethyl)acetamide, 1-N-dodecyl-2-pyrrolidone-5-carboxylic acid, 2-pentyl-2-oxo-pyrrolidineacetic acid, 2-dodecyl-2-oxo-1-pyrrolidineacetic acid, 2-dodecyl-2-oxo-l-pyrrolidineacetic acid, 1-azacylioheptan-2-one-dodecylacetic acid, menthol, propylene glycol,

glycerol monostearate, sorbitol monolaurate, glycerol dilaurate, tocopherol acetate, phosphatidyl choline, glycerol, polyethyleneglycol, a monoglyceride, a diglyceride, a triglyceride, lecithin, or sodium lauryl sulfate.

66. The formulation of any one of claims 37–65, wherein the formulation does not comprise a benzodiazepine.

67. The formulation of any one of claims 37-66, wherein the seletracetam is dissolved in the liquid carrier.

68. The formulation of any one of claims 37 and 39-67, wherein the seletracetam is suspended in the liquid carrier, e.g. wherein the seletracetam is in the form of a pharmaceutically acceptable co-crystal.

69. A nasal spray device comprising seletracetam.

70. An oromucosal spray device comprising seletracetam.

71. The device of claim 69 or claim 70, comprising the formulation of any one of claims 37–68.

72. The device of any one of claims 69-71, wherein the device is a unit-dose device.

73. The device of any one of claims 69-71, wherein the device is a bi-dose device or a multi-dose device.

74. The device of any one of claims 69–73, wherein the device comprises a mechanical spray pump.

75. The device of claim 71, comprising a metered dose spray pump.

76. The device of any one of claims 69–75, configured to dispense 25 µL to 200 µL of the formulation of any one of claims 37–68 per actuation of the device.

77. The device of claim 76, configured to dispense about 50 µL, about 75 µL, about 100 µL, or about 160 µL of the formulation of any one of claims 37–68 per actuation of the device.

78. The device of claim 77, configured to dispense about 50 µL of the formulation of any one of claims 37–68 per actuation of the device.

79. The device of claim 64, configured to dispense about 100 µL of the formulation of any one of claims 25–56 per actuation of the device.

80. The device of any one of claims 69-79, wherein the seletracetam is in the form of a pharmaceutically acceptable co-crystal.

81. An orally disintegrating tablet comprising seletracetam.

82. The tablet of claim 81, wherein the seletracetam has a particle size of 20 nanometers to 10 micrometers.

83. The tablet of claim 81 or claim 82, further comprising an alkyl saccharide.

84. The tablet of claim 83, wherein the alkyl saccharide is sucrose mono-stearate, sucrose di-stearate, tetradecyl maltoside, dodecyl maltoside, tetradecyl maltoside, or sucrose dodecanoate.

85. The tablet of claim 83 or claim 84, wherein the concentration of the alkyl saccharide is 0.1 wt.% to 10 wt.%.

86. The tablet of any one of claims 81–85, further comprising hydroxyethyl cellulose, hydroxypropyl cellulose, fish gelatin, gelatin type A, or mannitol.

87. The tablet of any one of claims 81–86, further comprising a coloring agent.

88. The tablet of claim 87, wherein the coloring agent comprises a titanium oxide or an iron oxide.

89. The tablet of any one of claims 81–88, further comprising a preservative.

90. The tablet of claim 89, wherein the preservative comprises sodium bisulfite, edetate disodium, sodium bisulfate, sodium thiosulfate, benzalkonium chloride, benzethonium chloride, chlorobutanol, thimerosal, phenylmercuric acetate, benzyl alcohol, phenylcarbinol, phenylmercuric nitrate, methylparaben, propylparaben, polyvinyl alcohol, phenylethyl alcohol, sodium benzoate, benzoic acid, phenyl ethyl alcohol, or ethylenediaminetetraacetic acid (EDTA).

91. The tablet of any one of claims 81–90, further comprising a flavoring agent, a sweetener, an odorant, or a taste-masking agent.

92. The tablet of claim 91, wherein the tablet comprises a flavoring agent, wherein the flavoring agent comprises vanilla extract, cinnamon, ginger, vanillin, linalool, coumarin, or a citrus oil.

93. The tablet of claim 91 or claim 92, wherein the tablet comprises a sweetener, wherein the sweetener comprises sucrose, xylitol, sodium saccharin, cyclamate, high fructose corn syrup, aspartame, acesulfame K, thaumatin, or stevia.

94. The tablet of any one of claims 91–93, wherein the tablet comprises a taste-masking agent, wherein the taste-masking agent comprises sodium chloride, citric acid, or sodium bicarbonate.

95. The tablet of any one of claims 81–94, further comprising a mucoadhesive agent.

96. The tablet of claim 95, wherein the mucoadhesive agent comprises hydroxyethyl cellulose, hydroxypropyl cellulose, dodecyl maltoside, sucrose dodecanoate, fish gelatin, gelatin type A, mannitol, or hyaluronic acid.

97. The tablet of claim 95 or claim 96, wherein the concentration of the mucoadhesive agent is 0.05% to 3.0% (w/w).

98. The tablet of any one of claims 81–97, further comprising an antioxidant.

99. The tablet of claim 98, wherein the antioxidant comprises ascorbic acid, sodium bisulfite, butylated hydroxytoluene, sodium metabisulfite, or tocopherol.

100. The tablet of any one of claims 81–99, further comprising a penetration enhancer.

101. The tablet of claim 100, wherein the penetration enhancer comprises dodecyl maltoside, tetradecyl maltoside, a bile salt, sodium dodecyl sulfate (SDS), dimethyl sulfoxide (DMSO), N-lauroyl sacrcosine, sorbitan monolaurate, stearyl methacrylate, N-dodecylazacyclohcptan-2-one, N-dodecyl-2-pyrrolidinone, N-dodecyl-2-piperidinone, 2-(1-nonyl)-1,3-dioxolane, N-(2-methoxymethyl) dodecylamine, N-dodecylethanolamine, N-dodecyl-N-(2-methoxymethyl)acetamide, 1-N-dodecyl-2-pyrrolidone-5-carboxylic acid, 2-pentyl-2-oxo-pyrrolidineacetic acid, 2-dodecyl-2-oxo-1-pyrrolidineacetic acid, 2-dodecyl-2-oxo-l-pyrrolidineacetic acid, 1-azacylioheptan-2-one-dodecylacetic acid, menthol, propylene glycol, glycerol monostearate, sorbitol monolaurate, glycerol dilaurate, tocopherol acetate, phosphatidyl

choline, glycerol, polyethyleneglycol, a monoglyceride, a diglyceride, a triglyceride, lecithin, or sodium lauryl sulfate.

102. The tablet of any one of claims 81–101, wherein the tablet does not comprise a benzodiazepine.

103. The tablet of any one of claims 81-102, wherein the seletracetam is in the form of a pharmaceutically acceptable co-crystal.

104. A mucoadhesive film comprising seletracetam.

105. The film of claim 104, further comprising a polymer comprising methyl cellulose, hydroxypropyl cellulose, carboxymethylcellulose, cellulose acetate, ethylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, an alginate, a gelatin, pullulan, pectin, locust bean gum, xanthan gum, sodium alginate, gum Arabic, nitrocellulose, a poly(ethylene oxide), a polyoxypropylene, or a polyvinylpyrrolidone.

106. The film of claim 105, wherein the polymer comprises ethylcellulose, poly(ethylene oxide), or hydroxypropyl cellulose.

107. The film of any one of claims 104–106, further comprising a coloring agent.

108. The film of claim 107, wherein the coloring agent comprises a titanium oxide or an iron oxide.

109. The film of any one of claims 104–108, wherein the film is a monolayer film.

110. The film of any one of claims 104–108, wherein the film is a bilayer film.

111. The film of any one of claims 104–108, wherein the film comprises at least three layers.

112. The film of claim 110 or claim 111, wherein the film comprises a first layer comprising seletracetam and a second layer comprising a base.

113. The film of claim 112, wherein the base comprises a polyamine, calcium hydroxide, magnesium hydroxide, potassium hydroxide, sodium hydroxide, calcium carbonate, iron carbonate, magnesium carbonate, zinc carbonate, sodium acetate, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, sodium phosphate monobasic, sodium

phosphate dibasic, sodium phosphate tribasic, potassium phosphate monobasic, potassium phosphate dibasic, or potassium phosphate tribasic.

114. The film of claim 113, wherein the base comprises a polyamine, wherein the polyamine comprises dimethylaminoethyl-acrylate, dimethylaminoethyl-methacrylate, dimethylaminopropyl-acrylate, dimethylaminpropyl-methacrylate, chitosan, polyethyleimine, polylysine, polyvinylimidazole, or polyvinylamine.

115. The film of any one of claims 104–114, further comprising a preservative.

116. The film of claim 115, wherein the preservative comprises sodium bisulfite, edetate disodium, sodium bisulfate, sodium thiosulfate, benzalkonium chloride, benzethonium chloride, chlorobutanol, thimerosal, phenylmercuric acetate, benzyl alcohol, phenylcarbinol, phenylmercuric nitrate, methylparaben, propylparaben, polyvinyl alcohol, phenylethyl alcohol, sodium benzoate, benzoic acid, phenyl ethyl alcohol, or ethylenediaminetetraacetic acid (EDTA).

117. The film of any one of claims 104–116, further comprising a flavoring agent, a sweetener, an odorant, or a taste-masking agent.

118. The film of claim 117, wherein the film comprises a flavoring agent, wherein the flavoring agent comprises vanilla extract, cinnamon, ginger, vanillin, linalool, coumarin, or a citrus oil.

119. The film of claim 117 or claim 118, wherein the film comprises a sweetener, wherein the sweetener comprises sucrose, xylitol, sodium saccharin, cyclamate, high fructose corn syrup, aspartame, acesulfame K, thaumatin, or stevia.

120. The film of any one of claims 116–119, wherein the film comprises a taste-masking agent, wherein the taste-masking agent comprises sodium chloride, citric acid, or sodium bicarbonate.

121. The film of any one of claims 104–120, further comprising a mucoadhesive agent.

122. The film of claim 121, wherein the mucoadhesive agent comprises hydroxyethyl cellulose, hydroxypropyl cellulose, dodecyl maltoside, sucrose dodecanoate, fish gelatin, gelatin type A, mannitol, or hyaluronic acid.

123. The film of claim 121 or claim 122, wherein the concentration of the mucoadhesive agent is 0.05% to 3.0% (w/w).

124. The film of any one of claims 104–123, further comprising an antioxidant.

125. The film of claim 124, wherein the antioxidant comprises ascorbic acid, sodium bisulfite, butylated hydroxytoluene, sodium metabisulfite, or tocopherol.

126. The film of any one of claims 104–125, further comprising a penetration enhancer.

127. The film of claim 126, wherein the penetration enhancer comprises dodecyl maltoside, tetradecyl maltoside, a bile salt, sodium dodecyl sulfate (SDS), dimethyl sulfoxide (DMSO), N-lauroyl sacrcosine, sorbitan monolaurate, stearyl methacrylate, N-dodecylazacyclohcptan-2-one, N-dodecyl-2-pyrrolidinone, N-dodecyl-2-piperidinone, 2-(1-nonyl)-1,3-dioxolane, N-(2-methoxymethyl) dodecylamine, N-dodecylethanolamine, N-dodecyl-N-(2-methoxymethyl)acetamide, 1-N-dodecyl-2-pyrrolidone-5-carboxylic acid, 2-pentyl-2-oxo-pyrrolidineacetic acid, 2-dodecyl-2-oxo-1-pyrrolidineacetic acid, 2-dodecyl-2-oxo-l-pyrrolidineacetic acid, 1-azacylioheptan-2-one-dodecylacetic acid, menthol, propylene glycol, glycerol monostearate, sorbitol monolaurate, glycerol dilaurate, tocopherol acetate, phosphatidyl choline, glycerol, polyethyleneglycol, a monoglyceride, a diglyceride, a triglyceride, lecithin, or sodium lauryl sulfate.

128. The film of any one of claims 104–127, wherein the mixture does not comprise a benzodiazepine.

129. The film of any one of claims 104-128, wherein the seletracetam is in the form of a pharmaceutically acceptable co-crystal.