# FDA Briefing Document

# Pharmacy Compounding Advisory Committee (PCAC) Meeting

# October 29, 2024

The attached package contains background information prepared by the Food and Drug Administration (FDA or Agency) for the panel members of the Pharmacy Compounding Advisory Committee (advisory committee). We are bringing certain compounding issues to this advisory committee to obtain the advisory committee's advice. The background package may not include all issues relevant to the final committee recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

# L-Theanine

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# FDA Evaluation of L-Theanine

DATE: 7/5/2024

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TO: Pharmacy Compounding Advisory Committee

SUBJECT: Evaluation of L-theanine for Inclusion on the 503A Bulk Drug Substances List

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## I. INTRODUCTION

L-theanine was nominated for inclusion on the list of bulk drug substances that can be used in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act).[1] L-theanine was evaluated for the following uses: sleep disorders and anxiety disorders.[2,3]

L-theanine products proposed in the nominations are:

- 2.5 mg tablet for sublingual (SL) route of administration (ROA)
- 10% cream for topical ROA
- 75 mg vial (10 mg/mL) solution for subcutaneous (SC)/intramuscular (IM) injection ROA
- 50 mg, 100 mg, and 200 mg capsules for oral ROA

There is no applicable United States Pharmacopeia (USP) or National Formulary (NF) drug substance monograph for L-theanine, and L-theanine is not a component of an FDA-approved drug.

We have evaluated publicly available data on the physicochemical characteristics, historical use, effectiveness, and safety, in compounding of this substance. For the reasons discussed below, we believe the evaluation criteria weigh against placing L-theanine on the list of bulk drug substances that can be used to compound drug products in accordance with section 503A of the FD&C Act (503A Bulks List).

## II. EVALUATION CRITERIA

### A. Is the substance well-characterized, physically, and chemically?[4]

[1] The nomination evaluated in this memo includes: nomination from Wells Pharmacy Network for L-theanine (Document ID: FDA-2015-N-3534-0304 attachment 2) and can be accessed at: https://www.regulations.gov/document/FDA-2015-N-3534-0304. Accessed 9/22/2023.

[2] We have explained that it is necessary to evaluate a nominated bulk drug substance in the context of the uses proposed for compounded drug products that include the substance, though we acknowledge that inclusion of a substance on the 503A Bulks List may not be limited to a specific use. See 84 FR 4696, 4701.

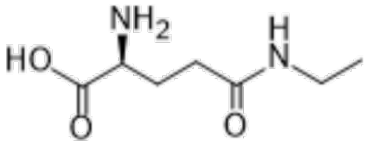
[3] L-theanine was nominated for the use "sleep, anxiety, relaxation, calming." The nominated use "sleep" is not a medical condition, but because the reference submitted by the nominator refers to "sleep disorders" which are medical conditions, we will evaluate L-theanine for sleep disorders. The nominated uses "anxiety, relaxation and calming" are not medical conditions. These will be considered under the group of medical conditions "anxiety disorders."

[4] Among the conditions that must be met for a drug compounded using bulk drug substances to be eligible for the exemptions in section 503A of the FD&C Act is that the bulk drug substances are manufactured by an establishment that is registered under section 510 of the FD&C Act and that each bulk drug substance is accompanied by a valid certificate of analysis. Sections 503A(b)(1)(A)(ii) and (iii). A bulk drug substance is deemed to be adulterated if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice. Section 501(a)(2)(B).

As noted above, there is no applicable USP monograph for L-theanine drug substance. We reviewed physical and chemical characterization related information provided by the nominators. Additionally, databases such as SciFinder, Analytical Profiles of Drug Substances, PubMed, the European Pharmacopoeia, and the USP/NF were searched for information on L-theanine. The information below summarizes what FDA found and assessed in these databases as well as in the nomination.

L-theanine (γ-glutamylethylamide or N-ethyl-L-glutamine) is a non-proteinogenic amino acid present almost exclusively in the tea plant (*Camellia sinensis*). The molecular formula of L-theanine is $C_7H_{14}N_2O_3$ and its molecular weight is 174.200 g/mol. Figure 1 shows the structure of L-theanine.

**Figure 1. Structure of L-theanine.**




The nominator provided the following certificate of analysis (CoA) for L-theanine with testing attribute results, such as identification, assay, specific rotation, residual solvents, and microorganism. There are no testing results for the control on impurities or endotoxins, which are the critical quality control attributes for the proposed dosage forms, especially for SC/IM use. Specifically, not controlling for impurities can lead to dosing of toxic substances and endotoxin testing allows for sterility assurance.

| TESTS | SPECIFICATIONS | RESULTS |
|---|---|---|
| ASSAY ON DRIED BASIS | 98.00 - 102.00 % | 99.63 % |
| DESCRIPTION | White to off-white, odourless, crystalline powder. | CONFORMS |
| IDENTIFICATION <197A>** | IR: Reference to standard spectrum. | POSITIVE |
| BULK DENSITY | To be reported. | 0.24 g/ml |
| TAPPED DENSITY | To be reported. | 0.48 g/ml |
| SPECIFIC ROTATION | +7.5° to +8.5° | + 7.96° |
| MELTING POINT | 200° - 210 °C | 202.4° - 202.6 °C |
| pH | 5.0 - 6.0 | 5.7 |
| CHLORIDE | <= 0.02 % | < 0.02 % |
| IRON | <= 0.001 % | < 0.001 % |
| LOSS ON DRYING | <= 1.00 % | 0.24 % |
| RESIDUE ON IGNITION | <= 0.20 % | 0.07 % |
| ELEMENTAL IMPURITIES <232>* | Meets the requirements | CONFORMS |
| TOTAL PLATE COUNT | <= 1000 cfu/g | < 1000 cfu/g |
| YEAST AND MOLD | <= 100 cfu/g | < 100 cfu/g |
| ABSENCE OF SPECIFIED MICROORGANISMS | Meets the requirements for the absence of:<br>• Staphylococcus aureus<br>• E.coli<br>• Salmonella<br>• Coliforms | CONFORMS |
| PARTICLE SIZE | 90 % through 60 mesh. | CONFORMS |
| RESIDUAL SOLVENTS | Meets the requirements | CONFORMS |
| SOLUBILITY | Very easily soluble in water. | |
| **PACKAGING AND STORAGE** | Preserve in tight, light-resistant containers. | |

*1. Stability of the active pharmaceutical ingredient (API) and likely dosage forms*

Based on the CoA the nominator provided the bulk drug substance should be preserved in tight, light-resistant containers.

It was reported by a supplier that L-theanine is stable for 2 years at 2-8°C from date of purchase. Literature reports suggest that solutions in distilled water may be stored at -20°C for up to 2 months.[5]

Theanine was isolated from tea leaves as L-form. Therefore, theanine generally refers to L-enantiomer and can be used interchangeably with L-theanine. It is reported that theanine can be broken down into glutamic acid and ethylamine in nature. One study investigated the hydrolysis of theanine at different pH values (pH 3, 7, and 11) using 0.1% triethylammonium acetate buffer. Amount of glutamic acid formed with respect to loss in theanine was reported over a period of

[5] https://www.chemicalbook.com/ChemicalProductProperty_EN_CB1485976.htm. Accessed December 18, 2023.

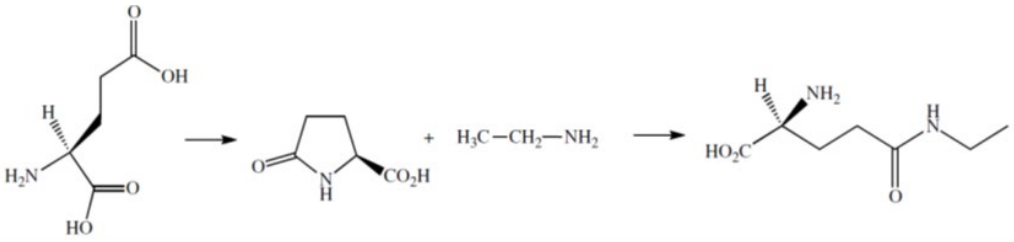
336 hours. The results indicated that there was little difference in hydrolysis of theanine between pH 3 and 7. However, the samples at pH 11 showed a far greater amount of hydrolysis (Ekborg-Ott et al. 1997). Therefore, proposed L-theanine product(s) should not be compounded as basic solution to prevent the hydrolysis of L-theanine.

*2. Probable routes of API synthesis*

L-theanine was first isolated and identified from green tea leaves in 1949 (Sakato 1949) and later also isolated from the mushroom, *Xerocomus badius* (Casimir et al. 1960).

Theanine was first chemically synthesized in 1942 by treating pyrrolidone-5-carboxylic acid with aqueous ethylamine for 20 days at 37°C with a yield of 90 g/kg (Lichtenstein 1942). Since then, several other synthetic approaches have been developed, including the reaction of γ-benzyl glutamate in the presence of trityl chloride and ethylamine (339 g/kg) (Kawagishi et al. 1992) and a two-step approach involving initial dehydration of L-glutamic acid to L-pyrrolidone carboxylic acid followed by ring opening in the presence of ethylamine to yield theanine (374 g/kg) (Figure 2) (Yan et al. 2003).

**Figure 2. Chemical Synthesis of L-theanine from L-glutamic Acid.**

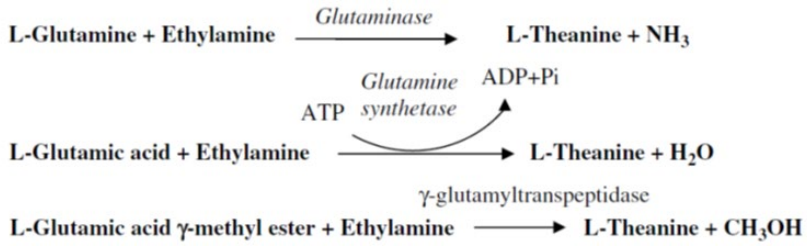



More recently, theanine was produced in four steps starting from commercially available *N*-phthaloyl-L-glutamic acid, which was dehydrated to the corresponding cyclic anhydride by reaction with acetic anhydride and then the ring was opened by reaction with ethylamine. Subsequent deprotection of the amine unit with hydrazine hydrate gave theanine with a 700 g/kg overall yield (Gu et al. 2004).

The reaction generally does not produce only the L(S)- form, but a racemic mixture (Gu et al. 2004; Mu et al. 2015). Therefore, the alternative biological enzymatic synthesis has been explored to form only L-theanine.

The following biosynthetic approaches have been developed using bacterial enzymes such as glutaminase (Nandakumar et al. 2003), glutamine synthetase (Miyake et al. 2009), and γ - glutamyl transpeptidase (Zhang et al. 2010) from *Escherichia coli* as well as other bacteria to synthesize theanine (Figure 3).

**Figure 3. Biosynthesis of L-theanine Using Bacterial Enzyme Systems.**




*3. Likely impurities*[6]

The likely impurity profile of L-theanine would be specific to and determined by the synthetic route used, which means that different synthetic routes used to produce L-theanine would result in different impurity profiles. The most likely impurities from above mentioned routes (Figures 2 and 3) would be the unreacted starting materials, intermediates, as well as reagents or residual solvents.

The CoA provided does not indicate which method was used to synthesize the nominated BDS. Also, the CoA doesn't include any tests, limits, or results for impurities, which would allow us to assess the nature and level of individual impurities or total impurities in the nominated BDS. A control of the individual and total impurities will be important to ensure suitability of the BDS for compounding.

*4. Physicochemical characteristics pertinent to product performance, such as particle size and polymorphism*

L-theanine is a white to off-white, odorless crystalline powder. It is soluble in water up to 20 mg/mL.[7] Therefore, the particle size is not considered a critical quality attribute that affects performance for the proposed dosage forms, including 5 mg sublingual tablet; 50 mg, 100 mg, and 200 mg capsules; 75 mg vial (10 mg/mL) injection; and solution (strength was not stated). For the 10% cream dosage form, the particle size is set in the CoA. There is lack of endotoxin testing limits set in the CoA. Endotoxin testing limits are needed to ensure sterility of the finished product, which is a concern for proposed injection dosage form.

*5. Any other information about the substance that may be relevant, such as whether the API is poorly characterized or difficult to characterize*

There is no other available information that is relevant to the BDS.

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[6] This evaluation contains a non-exhaustive list of potential impurities in the bulk drug substance and does not address fully the potential safety concerns associated with those impurities. The compounder should use the information about the impurities identified in the certificate of analysis accompanying the bulk drug substance to evaluate any potential safety and quality issues associated with impurities in a drug product compounded using that bulk drug substance taking in account the amount of the impurity, dose, route of administration, and chronicity of dosing. Available nonclinical toxicity data for likely impurities of concern (e.g., nitrosamines, potential mutagenic substances, and potential teratogenic substances) in the nominated bulk drug substance are discussed in the Nonclinical Assessment at Section D.1. as part of the safety assessment of the substance.

[7] https://www.chemicalbook.com/ChemicalProductProperty_EN_CB1485976.htm. Accessed December 18, 2023.

**Conclusions:** In summary, L-theanine is a non-protein amino acid. It is a white to off-white, odorless, crystalline powder and soluble in water. L-theanine powder is stable for 2 years at 2-8°C. Solutions in distilled water may be stored at -20°C for up to 2 months.

There is no information, either in the publicly available scientific literature or in the CoA provided by the nominator, about BDS related impurities and endotoxin testing, both of which are considered critical quality attributes for the quality control of the nominated BDS used for the proposed dosage forms. The endotoxin testing control is especially important for compounding sterile injectable dosage forms. Therefore, the nominated BDS, L-theanine, is not well characterized from the physical and chemical characterization perspective.

**B. Has the substance been used historically in compounding?**

This evaluation focuses on L-theanine and its use in sleep disorders and anxiety disorders (which includes relaxation and calming); however, FDA also searched generally for information on the historical use of L-theanine in compounding.

L-theanine is marketed online in the United States as an ingredient in oral dietary supplement products formulated as a powder[8], a gummy[9], a tablet[10], a capsule[11], and a liquid[12]. Oral L-theanine was determined to be Generally Recognized as Safe (GRAS)[13] and is marketed in the United States as an ingredient in fruit juices and drinks, non-herbal teas, sports beverages, specialty bottled waters, chocolate bars and chews, hard candies, and breath mints, and chewing gum at a level up to 250 mg of L-theanine per serving.[14]

While L-theanine may be used as a dietary supplement, food, or drug product, for purposes of this evaluation, FDA assessed the literature support related to the use of L-theanine as a drug

[8] https://www.bulksupplements.com/products/ltheanine. Accessed 12/8/2023.
[9] https://brainmd.com/l-theanine-gummies. Accessed 6/10/2024.
[10] https://www.naturemade.com/products/l-theanine-200-mg-chewable-tablets?variant=41237034270859. Accessed 12/8/2023.
[11] https://www.bulksupplements.com/products/l-theanine-pills. Accessed 12/8/2023.
[12] https://numedica.com/catalog/NM965. Accessed 12/8/2023.
[13] Under sections 201(s) and 409 of the FD&C Act (21 U.S.C. 321(s) and 348), any substance that is intentionally added to food is a food additive that is subject to premarket review and approval by FDA, unless the substance is generally recognized, among qualified experts, as having been adequately shown to be safe under the conditions of its intended use, or unless the use of the substance is otherwise excepted from the definition of a food additive. For more information, see https://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/. Accessed on 12/8/2023.

GRAS determinations for food are made under food safety standards and thus are not dispositive when considering the use of a substance as an active ingredient in a compounded drug product. A substance that is safe when used as a food might not be safe as an active ingredient in a drug product, for example, when used for a route of administration other than oral. Moreover, such a GRAS determination does not indicate that a substance would have any effectiveness for a particular proposed use when used in a compounded drug product. We note, however, that FDA has considered CFSAN's GRAS notices and their implications in reviews completed to date where relevant, for example, in our review of safety or physical and chemical properties.
https://www.federalregister.gov/documents/2019/02/19/2019-02367/list-of-bulk-drug-substances-that-can-be-used-to-compound-drug-products-in-accordance-with-section#footnote-1-p4700. Accessed 12/8/2023.
[14] Re: GRAS Notice No. GRN 000209 available at: https://www.suntheanine.com/wp-content/uploads/2014/06/ST-FDA-GRAS.pdf. Accessed 12/8/2023.

product, e.g., studies looking at use to treat a specific disease state. Databases searched for information on L-theanine for this evaluation included PubMed, EMBASE, Natural Medicines, Google/Google Scholar, USP-NF, European Pharmacopoeia, Indian Pharmacopeia, Chinese Pharmacopoeia, and Japanese Pharmacopoeia.

*1. Length of time the substance has been used in compounding*

The nominator did not provide historical use data. Literature shows that L-theanine was first identified as an amide constituent of green tea in 1949 (Sakato 1949; Yoneda et al. 2020). According to outsourcing facility (OF) product reports submitted to FDA, multiple ingredient injection solution drug products containing L-theanine have been compounded within the United States since at least December 2017.[15]

*2. The medical condition(s) it has been used to treat*

A search of the Natural Medicines Database and publicly available literature conducted by FDA revealed articles in which oral L-theanine has been studied in human subjects for cognitive impairment (Park et al. 2011), age-related cognitive decline (Baba et al. 2021), anxiety (Hidese et al. 2019; Lu et al. 2004), attention deficit-hyperactivity disorder (ADHD) (Kahathuduwa et al. 2020), poor sleep quality in subjects with ADHD (Lyon et al. 2011), major depressive disorder (MDD) (Hidese et al. 2017, Shamabadi et al. 2023), generalized anxiety disorder (GAD) (Sarris et al. 2019, Mason 2001), influenza (Matsumoto et al. 2011), chemotherapy-induced diarrhea (Hamaguchi et al. 2020; Tsuchiya et al. 2016), insomnia (Thiagarajah et al. 2022), schizophrenia (Kardashev et al. 2018; Ritsner et al. 2011), Tourette's syndrome (Rizzo et al. 2022), and moderate to severe obsessive-compulsive disorder (OCD) (Nematizadeh et al. 2023). Many of these articles described the use of L-theanine in combination with other substances.

Some clinical studies use the terms L-theanine and theanine interchangeably. Several of these clinical studies appear to have evaluated the use of compounded formulations of L-theanine or theanine for various medical conditions. Examples include the following:

- Baba et al. 2021 studied L-theanine in age-related cognitive decline in Japan. Specifically, L-theanine as Suntheanine which contains ≥ 98% L-theanine "was encapsulated into hard No. 1 porcine gelatin capsules and used for the test." According to the authors, "Each theanine capsule contained 100.6 mg of l-theanine."
- Kahathuduwa et al. 2020 studied the use of L-theanine in combination with caffeine administered orally in patients with attention deficit hyperactivity disorder (ADHD) in the U.S. The authors stated, "L-Theanine and caffeine were purchased in purified powder form (PureBulk Inc., Roseburg, OR, USA) to prepare the solutions," … "doses were measured using a Gemini-20 milligram scale with a precision of 1 mg (American

[15] The Drug Quality and Security Act, signed into law on November 27, 2013, created a new section 503B in the Federal Food, Drug, and Cosmetic Act. Under section 503B, a compounder can become an outsourcing facility. Outsourcing facilities are required to provide FDA with a list of drugs they compounded during the previous six-month period upon initial registration and in June and December each year. This retrospective information does not identify drugs that outsourcing facilities intend to produce in the future. The outsourcing facility product report is available at: https://www.accessdata.fda.gov/scripts/cder/outsourcingfacility/index.cfm.

Weight Scales Inc., Cumming, GA, USA)" and "the solutions were made" … "by dissolving the doses of l-theanine and/or caffeine in a 100 mL aliquot of bottled water."

- Lyon et al. 2011 also studied the use of L-theanine for use in pediatric patients in Canada with disordered sleep in ADHD who "were required to take a total of four chewable tablets of L-theanine (two 100-mg tablets in the morning and two 100-mg tablets in the late afternoon after school [total of 400 mg L-theanine]) or placebo daily." According to the authors, "the formulation was produced as a chewable tablet" … "in two flavors (wild berry and tropical fruit)" because "it was thought that the children might have greater difficulty swallowing pills or tablets."

It is unknown whether a compounded oral L-theanine drug product was used in the studies that evaluated subjects with GAD, MDD, or OCD.

In addition, Cross et al. 2011 examined "Endotrex, … a sublingual liposomal spray formulation containing Suntheanine R (50 mg L-theanine per pump)" in a clinical trial in pediatric patients who exhibited behavioral/emotional difficulties as reported by their parents.

An internet search for compounded drug products containing L-theanine revealed that the "Institute for Beauty Wellness and Regenerative Medicine Spa," markets "De-stress," a multiple ingredient intramuscular injection containing "L-theanine, taurine, GABA, and magnesium… to de-stress and recharge." The website states, "this injection will help reduce stress and have you feeling more grounded, reducing irritability, and increasing relaxation in the body."[16]

The International Journal of Compounding (IJPC) published a formulation for preparing oral "Progesterone 100 mg, Melatonin 1 mg and L-Theanine 200 mg Slow-Release Capsules" that states the preparation "has been used for hormone replacement therapy [progesterone component] and as a sleep aid [L-theanine]."[17]

*3. How widespread its use has been*

The IJPC published a formulation for "Progesterone 100 mg, Melatonin 1 mg and L-Theanine 200 mg Slow-Release Capsules."[18,19]

According to OF product reports submitted to FDA, three OFs reported compounding multiple ingredient injection solution drug products containing L-theanine in combination with other substances, including taurine, magnesium chloride anhydrous, magnesium chloride tetrahydrate, gamma-aminobutyric acid, and gabapentin from December 2017 to June 2020.

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[16] Intramuscular injections - Destress. https://store.withdrnicole.com/intramuscular-injections.html. Accessed 06/27/2023.
[17] Progesterone 100 mg, Melatonin 1 mg and L-theanine 200 mg Slow-Release Capsules. https://ijpc.com/Abstracts/Abstract.cfm?ABS=4746 (Subscription required). Accessed 06/27/2023.
[18] Progesterone 100 mg, Melatonin 1 mg and L-theanine 200 mg Slow-Release Capsules. https://ijpc.com/Abstracts/Abstract.cfm?ABS=4746 (subscription required). Accessed 06/27/2023.
[19] The availability of a published formulation indicates that at one time there was, and potentially continues to be, interest in compounding products containing L-theanine, which provides additional insight into the historical use of L-theanine in compounding.

Results from an internet search for compounded drug products containing L-theanine revealed at least one compounding pharmacy within the United States compounding L-theanine.[20]

*4. Recognition of the substance in other countries or foreign pharmacopeias*

A search of the European Pharmacopoeia (11th Edition 11.3-11.5), and the Japanese Pharmacopoeia (18th Edition) did not find any monograph listings for L-theanine. In addition, the 2010 – 2020 version (10th edition 2015) of the Chinese Pharmacopoeia and the 2010 version of the Indian Pharmacopoeia also did not include any monograph listings for L-theanine.

**Conclusions:** L-theanine has been used in pharmacy compounding in the U.S. since at least 2017. Published literature suggests that studies were performed involving the use of drug products containing compounded L-theanine as an oral formulation for use in patients with age-related cognitive decline, ADHD, and disordered sleep both within and outside the United States. L-theanine has been advertised as a compounded oral formulation for patients with various conditions within the United States. According to OF product reports submitted to FDA, OFs prepared compounded multiple-ingredient injectable products containing L-theanine between December 2017 and June 2020. We found no evidence of compendial monographs in countries outside of the United States.

**C. Are there concerns about whether a substance is effective for a particular use?**

The following databases were consulted in the preparation of this section: PubMed, Embase, Cochrane Database of Systematic Reviews, ClinicalTrials.gov, professional healthcare organization websites, and various online clinical references and websites. In addition to a comprehensive review of pertinent information from these databases, this section provides a brief overview of sleep disorders and anxiety disorders, relevant regulatory history, and a discussion of the data on effectiveness for the proposed uses of L-theanine. The nominated use "sleep" is not a medical condition, but because the reference submitted by the nominator refers to "sleep disorders" which are medical conditions, we will evaluate L-theanine for sleep disorders. The nominated uses "anxiety, relaxation and calming" are not medical conditions. These will be considered under the group of medical conditions "anxiety disorders". Furthermore, the scope of discussions under sleep disorders and anxiety disorders was limited to conditions that discussed evaluation of L-theanine in the articles identified in the databases that were consulted. The nominator did not specify which population they intended to treat with L-theanine. The reference submitted by the nominator was for use in children. Because the nominator did not specify which population they intended to use L-theanine for and because treatments for sleep disorders and anxiety disorders are different in adults and children, we have included a discussion of the uses of L-theanine in both pediatric and adult populations for both sleep

[20] Magnesium Glycinate 200 mg, Melatonin 3 mg, Theanine 250 mg Oral Capsules. https://www.bayviewrx.com/formulas/Magnesium-Glycinate-200-mg-Melatonin-3-mg-Theanine-250-mg-Oral-Capsules-Insomnia-Anxiety-Restless-Leg-Syndrome-Fibromyalgia-Migraine-Prevention. Accessed 6/10/2024.

disorder and anxiety disorders. We evaluated L-theanine for sleep disorders and anxiety disorders and considered available data to support effectiveness.

### *1. **Sleep disorders***

Sleep outcomes and definitions discussed in the section:
The clinical studies discussed in this section include information for objective assessments for the sleep outcomes that were derived from either actigraphy and/or polysomnography. The following information was obtained from the referenced American Academy of Neurology (AAN) practice guideline published in 2020 (Buckley et al. 2020).

Sleep onset latency (SOL) refers to the amount of time from lights turned off until the onset of any sleep stage. Normal SOL in adults is less than 20 minutes. In children, sleep latency is estimated at 10–26 min, depending on study methods. Sleep latency does not change between childhood and adolescence (Zolovska and Shatkin 2013). Prolonged sleep latency would be characterized as difficulty falling asleep.

Night awakenings refers to the number of complete awakenings occurring after sleep initiation.

Total sleep time (TST) refers to sleep duration during a given sleep period time (usually at night). Reduced TST relates to prolonged SOL, night awakenings, and early-morning waking. Included studies compare TST changes with treatment rather than referencing age-specific sleep duration recommendations.

Sleep Cycle Characteristics:
The sleeping body cycles through regular sleep patterns of activity, known as the sleep cycle. Over the course of one night, the body goes through the sleep stages approximately every 90 minutes. Sleep stages last for different periods of time depending on the age of the sleeper. The first three sleep stages are categorized as non-REM sleep, and the fourth and final sleep stage is Rapid Eye Movement (REM) sleep. The amount of time that individuals sleep in a 24-hour period varies with age. Descriptions of the sleep stages and recommended sleep times for each age group are listed in Tables A and B in Appendix 1.

Sleep Disorders:
Sleep disorders encompass several different disorders that affect different parts of the normal sleep cycle. Sleepiness may manifest as irritability, behavioral changes, learning or attentional difficulties, or motor vehicle crashes (Esposito et al. 2019). Sleep disorders include insomnia, Rapid Eye Movement (REM) sleep disorders, obstructive sleep apnea (OSA), central disorders of hypersomnolence (such as narcolepsy), intrinsic (advanced sleep phase disorder) or extrinsic (jet lag) circadian rhythm sleep-wake disorders (CRSWDs), restless leg syndrome, and parasomnias (night terrors and sleepwalking). These disorders can occur in adults and children. Each of these disorders has different recommended treatments based on the pathophysiology of that condition. Definitions of these sleep disorders are provided in Table 1 below.

**Table 1. Definitions of Sleep Disorders**

| Sleep Disorder | Definition |
|---|---|
| Insomnia | Trouble initiating or maintaining sleep which is associated with daytime consequences and is not attributable to environmental circumstances or inadequate opportunity to sleep (Sateia et al. 2017) |
| REM Sleep Disorders | The atonia of REM sleep is lost, resulting in individuals acting out their dreams with potentially violent and injurious behaviors (Howell et al. 2023) |
| Obstructive Sleep Apnea | Episodes of complete collapse of the airway or partial collapse with an associated decrease in oxygen saturation or arousal from sleep. This disturbance results in fragmented, nonrestorative sleep.[21] |
| Central Disorders of Hypersomnolence[22] | Excessive daytime sleepiness (including episodes of irresistible sleepiness). Some patients with narcolepsy may experience episodes characterized by sudden loss of muscle tone. |
| Circadian Rhythm Sleep-Wake Disorders | Misalignment between the timing of the sleep and wake cycles generated by the endogenous circadian clock and that required in the new time zone or for a job that requires shift work (Morgenthaler et al. 2007) |
| Restless Leg Syndrome (RLS) | A neurological disorder that causes unpleasant or uncomfortable sensations in your legs and an irresistible urge to move them. Symptoms commonly occur in the late afternoon or evening hours and are often most intense at night when resting. RLS can severely disrupt sleep, making it difficult to fall asleep or return to sleep after waking up. Moving the legs or walking typically relieves the discomfort but the sensations often recur once the movement stops.[23] |
| Parasomnias | Talking, screaming, walking during sleep with difficulty arousing the person from the episode. The person may have little to no memory of the event afterwards.[24] |

To diagnose a specific sleep disorder, an assessment may be done to determine the primary cause and to rule out secondary causes, such as side effects of medications, substance abuse, psychiatric illnesses (such as depression and anxiety), or another previously undetected illness that causes pain or disrupts sleep (epilepsy, gastrointestinal disorder, pain, rheumatologic diseases, atopic dermatitis, pulmonary diseases such as asthma or chronic cough), and

[21] https://www.ncbi.nlm.nih.gov/books/NBK459252/. Accessed 10/17/2023.
[22] This group of disorders includes narcolepsy, Kleine-Levin Syndrome, hypersomnia due to Parkinson's or dementia with Lewy bodies, hypersomnia secondary to traumatic brain injury, myotonic dystrophy, brain tumors, infections, or multiple sclerosis (Maski et al. 2021).
[23] https://www.ninds.nih.gov/health-information/disorders/restless-legs-syndrome. Accessed on 7/5/2024.
[24] https://www.hopkinsmedicine.org/health/conditions-and-diseases/parasomnias-sleepwalking#:~:text=Sleep%20is%20divided%20into%20REM,early%20part%20of%20the%20night. Accessed 10/17/2023.

psychological or behavioral causes. For children with neurodevelopmental disorders (such as Attention-Deficit/Hyperactivity Disorder: ADHD), sleep disorders are more common and more severe compared with typically developing children. The sleep disorders observed in patients with neurodevelopmental disorders are reported to be complex and usually more difficult to treat than in subjects without neurodevelopmental disorders (Esposito et al. 2019).

Professional Society Guidelines:
The American Academy of Sleep Medicine (AASM) has published practice guidelines on the treatment of the different sleep disorders. As shown in Table C in Appendix 1, none of these practice guidelines discuss the use of L-theanine in adults or children.

FDA-approved drug products, such as those indicated for insomnia, evaluated endpoints such as sleep latency, sleep duration, sleep efficiency, and number of awakenings as recorded on polysomnogram and by patient report to establish efficacy in confirmatory clinical trials. FDA-approved products for OSA, narcolepsy, and shift work disorder (a type of circadian rhythm sleep-wake disorder) evaluated endpoints such as polysomnogram findings, the Multiple Sleep Latency Test[25], the Maintenance of Wakefulness Test[26], and the Epworth Sleepiness Scale[27].

a. Reports of trials, clinical evidence, and anecdotal reports of effectiveness, or lack of effectiveness, of the bulk drug substance

In our evaluation of effectiveness, we initially discuss data from the nominator-submitted publication for the context of use proposed for compounded drug products that include L-theanine for sleep disorders. The publication by Lyon et al. (2011) discussed L-theanine for sleep disorders in children with ADHD. Our analysis also included studies identified by FDA that evaluated L-theanine in adults with poor sleep quality.

In additional articles found by FDA, the population treated was children with ADHD without information on use of L-theanine for sleep disorders. ADHD was not a nominated use, and the articles did not include outcomes assessing sleep measures.

[25] The Multiple Sleep Latency Test (MSLT) checks for excessive daytime sleepiness by measuring how quickly you fall asleep in a quiet environment during the day. Also known as a daytime nap study, the MSLT is used to diagnose narcolepsy and idiopathic hypersomnia. https://sleepeducation.org/patients/multiple-sleep-latency-test/. Accessed on 10/23/2023.
[26] The Maintenance of Wakefulness Test (MWT) is used to measure how alert you are during the day. It shows whether you can stay awake for a defined period of time. The test is based on the idea that, in some cases, your ability to stay awake may be more important than how fast you fall asleep. This is an indicator of how well you can function and remain alert in quiet times of inactivity. https://sleepeducation.org/patients/maintenance-of-wakefulness-test/. Accessed on 10/23/2023.
[27] The ESS is a self-administered questionnaire with 8 questions. Respondents are asked to rate, on a 4-point scale (0-3), their usual chances of dozing off or falling asleep while engaged in eight different activities. The ESS score (the sum of 8 item scores, 0-3) can range from 0 to 24. The higher the ESS score, the higher that person's average sleep propensity in daily life (ASP), or their 'daytime sleepiness'. https://epworthsleepinessscale.com/about-the-ess/. Accessed on 10/23/2023.

Lyon et al. 2011:
In this double blind, placebo-controlled trial, ninety-eight 8–12-year-old boys with ADHD[28, 29] were randomized to receive either oral L-theanine (200 mg BID) or placebo (which contained lactose) for 6 weeks.[30] The purpose of the present study was to investigate improvements on objective (actigraphy) and subjective (Pediatric Sleep Questionnaire) measures of sleep quality in boys with ADHD and whether L-theanine would result in a significant change from baseline in objective sleep quality measured by actigraphy. A major deficiency of the study is that it does not identify the primary and secondary endpoints nor provide a conventional statistical analysis plan. The authors note that "given that there are a large number of comparisons, an alpha of 0.01 was employed." It is unclear how many endpoints were evaluated in total. Sleep quality was measured with an actigraphy watch for five consecutive nights at baseline and at the end of six weeks, and a Pediatric Sleep Questionnaire (PSQ)[31] was completed by the subjects' parents at baseline and at the end of six weeks. Baseline measures on actigraphy or PSQ and core ADHD symptoms were not reported.

Although the authors did not publish numerical data on actigraphy measures, there were graphical representations for the outcomes considered in the study (Figure 4). There was no significant difference between treatment groups in sleep latency or sleep duration. The graphs shown for actigraphy measures in Figure 4, appear to compare the change from baseline to end of study actigraphy results between the L-theanine and placebo groups. The study authors report that participants in the L-theanine study arm spent an increased percent of time in restful sleep (sleep efficiency 80% compared to 76% in placebo), decreased sleep activity (fewer bouts of nocturnal activity), and on average 15 fewer minutes spent awake after onset of sleep compared to the placebo group (Figure 4). None of the p values calculated for the endpoints in figure met the 0.01 level of significance. The authors state that PSQ data did not correlate with the actigraphy data, but the PSQ data was not discussed further. Data was analyzed for the 93 subjects who completed the study, and it is unclear when and why the other subjects did not complete the study and which treatment group they were in. This may have confounded the results.

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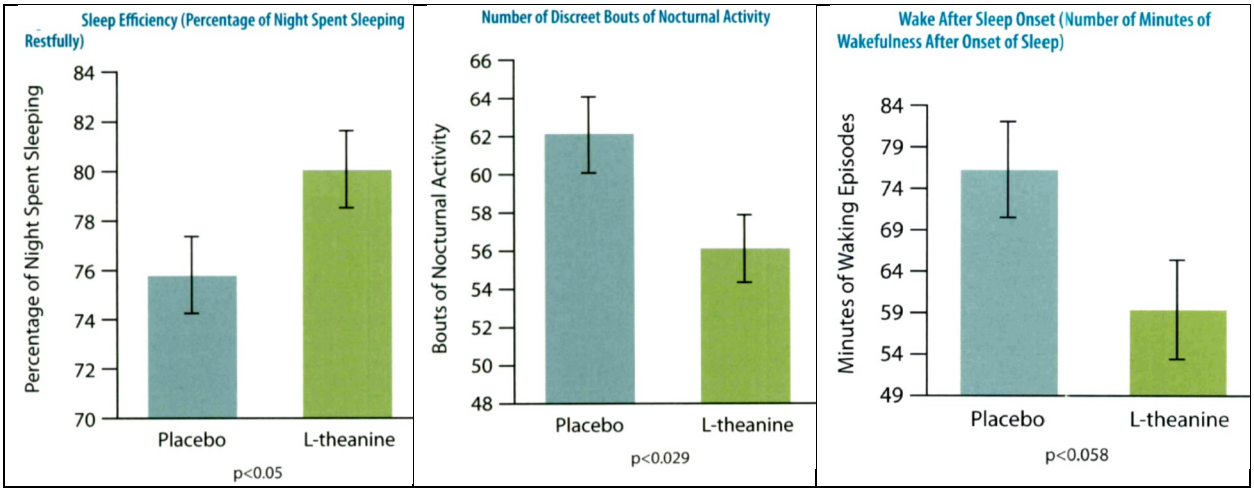
[28] A neurodevelopmental disorder characterized by a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development (DSM-5-TR).

[29] L-theanine was not used as a treatment for the core ADHD symptoms in this study. L-theanine was not discussed in the ADHD treatment guidelines for adults or children (Post and Kurlansik 2012; Wolraich et al. 2019). Two other studies found by FDA (Kahathaduwa et al. 2020 and Cross et al. 2011) examined treatment of ADHD symptoms in children who received L-theanine, but these studies did not evaluate sleep endpoints in this population. No studies were found in which L-theanine was used for the treatment of sleep disorders in adults with ADHD.

[30] The actigraphic sleep measures included sleep efficiency (percentage of night spent sleeping restfully), number of discreet bouts of nocturnal activity, number of minutes of wakefulness after onset of sleep (wake after sleep onset [WASO]), sleep latency (time to fall asleep), and sleep duration (total sleep time).

[31] The PSQ (Buysse et al. 1988) contains 22 symptom items that ask about snoring frequency, loud snoring, observed apneas, difficulty breathing during sleep, daytime sleepiness, inattentive or hyperactive behavior, and other pediatric OSA features.
It was standardized in children aged 2±18 years who had polysomnographically-confirmed sleep disordered breathing. Scores >0.33 are considered positive and suggestive of high risk for a pediatric sleep-related breathing disorder. https://www.thoracic.org/members/assemblies/assemblies/srn/questionaires/psq.php. Accessed 10/23/2023.

**Figure 4. Actigraphy measures of sleep quality**




Although the majority of participants were not being treated for ADHD at the time of the study (28% in the L-theanine group and 29% in the placebo group were on stimulants), the authors did not show results by subgroup to discuss whether being on a stimulant (medications known to adversely affect sleep) had an effect on the study outcomes. They also did not discuss which type of stimulants the subjects were taking (long vs. short acting stimulants) and when these were being given. It is also unclear whether the authors controlled for environmental factors or sleep hygiene behaviors that might have affected sleep, and which could have confounded the results of the study if there were differences in these factors between treatment groups. Compliance with wearing the actigraph watch was not reported.

Although the authors report slight changes in some actigraphy measures in this small study that examined sleep quality in boys with ADHD, they did not achieve the pre-specified level of significance and it is unclear whether these changes are clinically meaningful. Because no female subjects with ADHD were included, it is unclear whether these results are generalizable to a larger population of children with ADHD and sleep disorders. Because it is unclear if any of the study participants had a primary sleep disorder, it is unclear if the study findings can be generalized to populations with primary sleep disorders who do not have ADHD. It is unclear whether the changes on sleep measures will be observed with long-term use of L-theanine. As observed by the authors, it remains to be determined how the observed changes will translate into measurable positive changes in symptoms of ADHD. The authors note that a longer duration study is needed with robust measures of mood, cognition, and behavioral change.

Two additional studies discussed the use of L-theanine in adults with poor sleep quality.

Thiagarajah et al. 2022:
This randomized, double-blind, placebo-controlled, crossover study investigated the effects of RLX2 (a substance containing 150 mg alpha-s1-casein tryptic hydrolysate and 50 mg L-theanine) in working adults[32] affected by poor sleep quality (as defined by a score of greater than

[32] Study subjects were randomly selected from the academic staff at a university in Malaysia. Subjects were then screened for study inclusion using the PSQI.

5 on the Pittsburgh Sleep Quality Index: PSQI).[33] Thirty-nine adults received either RLX2 or placebo for four weeks. Subjective sleep assessment via the PSQI, heart rate, blood pressure, salivary cortisol by high-performance liquid chromatography method and alpha power of awake electroencephalogram (EEG) were studied. Sleep duration and sleep habitual efficiency were reportedly improved in the RLX2 group vs placebo. Limitations of this study include its small sample size, and the absence of the use of objective measures to assess sleep outcomes. It is difficult to determine the contribution of L-theanine to the study outcomes because L-theanine was given with another substance as part of the study intervention. Additionally, the study subjects reported having poor sleep quality, but the authors do not report whether any of the study subjects had a primary sleep disorder. It is unknown if study subjects were taking other medications that may have affected their sleep.

Ota et al. 2015:
Seventeen adults with chronic schizophrenia and twenty-two age and sex matched healthy subjects were selected for the open label study. L-theanine (Suntheanine) 250 mg/day for 8 weeks was added to the subjects' current treatment for schizophrenia. Outcomes measured included: changes in Positive and Negative Symptoms Score (PANSS), sleep quality measured using PSQI, and changes in glutamate and glutamine in the brain on magnetic resonance spectroscopy (MRS). The authors reported that L-theanine ameliorated positive symptoms of schizophrenia and improved sleep quality.

Limitations of this study include the small sample size and lack of a control group. It is not clear what other medications study subjects were taking during the study, and whether any of these medications were intended to treat sleep difficulties or whether the concomitant treatment for schizophrenia may have affected sleep as a side effect. Other significant deficiencies include the failure to measure objective assessments of sleep, and it is unclear whether any of the study subjects had a primary sleep disorder. Because this was a small study involving study subjects with schizophrenia, it is unclear whether study results would be generalizable to a larger population of patients with primary sleep disorders.

We were unable to find studies in which L-theanine was studied to treat many of the primary sleep disorders. Although we found references in which L-theanine was studied to treat sleep quality, these studies examined subjects who had other underlying comorbidities or medical conditions, or who were taking concomitant medications. These factors confound the study results, as symptoms such as poor sleep quality may be due to another underlying medical condition and not to a primary sleep disorder. When study subjects receive multiple interventions during a study, it is not possible to conclude which intervention is reflected in the study results.

b. Whether the product compounded with this bulk drug substance is intended to be used in a serious or life-threatening disease

[33] The Pittsburgh Sleep Quality Index (PSQI) is a self-rated questionnaire which assesses sleep quality and disturbances over a 1-month time interval. Nineteen individual items generate seven "component" scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction.

Some of the primary sleep disorders can be serious. Sleep disorders negatively affect sleep and quality of life of affected individuals and their families. They can have a detrimental impact on the physical and emotional well-being of both patients and other family members; for example, children's sleep disturbance is associated with heightened levels of parental stress and irritability (Parker et al. 2019). Disordered sleep is also associated with daytime behavioral disturbances, increased injury risk, obesity, and poor academic performance in pediatric populations (Buckley et al. 2020).

c. Therapies that have been used for the condition(s) under consideration

There are FDA-approved drug products and/or over-the-counter (OTC) monograph drug products indicated for the same medical condition as those proposed for the L-theanine compounded drug product(s).[34] Primary sleep disorders in adults for which FDA-approved therapies exist are listed in Table 2 below.

**Table 2. FDA-Approved Therapies for Primary Sleep Disorders in Adults.**[35, 36]

| Sleep Disorder | FDA-Approved Therapy |
|---|---|
| Insomnia | Ambien, Elduar (zolpidem)<br>Belsomra (suvorexant)<br>Dayvigo (lemborexant)<br>Doral (quazepam)<br>Estazolam<br>Flurazepam<br>Halcion (triazolam)<br>Hetlioz (tasimelteon)<br>Lunesta (eszopiclone)<br>Quviviq (daridorexant)<br>Restoril (temazepam)<br>Rozerem (ramelteon)<br>Seconal (secobarbital)<br>Silenor (doxepin)<br>Sonata (zaleplon) |
| Obstructive Sleep Apnea | Nuvigil (armodafinil)<br>Provigil (modafinil)<br>Sunosi (solriamfetol) |
| Circadian Rhythm Sleep-Wake Disorders | Nuvigil (armodafinil)<br>Provigil (modafinil) |
| Restless Leg Syndrome | Ropinirole |

[34] FDA considers the existence of FDA-approved or OTC monograph drug products to treat the same condition as that proposed for the nomination relevant to FDA's consideration of the safety criterion, to the extent there may be therapies that have been demonstrated to be safe under the conditions of use set forth in the approved labeling. See 84 FR 4696.

[35] Information about the drugs listed in this table can be found at the following website: https://fdalabel.fda.gov/fdalabel/ui/search. Accessed 10/23/2023.

[36] https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/sleep-disorder-sedative-hypnotic-drug-information. Accessed 9/1/2023.

For some primary sleep disorders, medications that induce sleep can worsen the condition. There are no FDA-approved treatments for insomnia in the pediatric population. FDA-approved drugs are sometimes prescribed off-label for the management of some sleep disorders in children and adolescents (e.g., antihistamines, a-adrenergic agonists like clonidine, antidepressants, antipsychotics) for their sedative side effects without sufficient information on their efficacy, safety, or the dosing regimen in these populations (Gringras et al. 2017). The dietary supplement melatonin is also sometimes used for sleep in pediatric populations (Ivanenko et al. 2021, Gringras et al. 2017).

The following includes currently available OTC monograph drug products used to treat individuals older than 12 years of age with occasional sleeplessness not lasting more than 2 weeks: Benadryl (diphenhydramine hydrochloride).[37]

Non-pharmacological interventions for sleep disorders include cognitive behavioral therapy, behavioral interventions, and maintaining adequate sleep hygiene. Obstructive sleep apnea treatment options may also include surgery to remove the tonsils and adenoids in children, continuous positive airway pressure (CPAP), or oral mechanical devices (Ivanenko et al. 2021).

Conclusions for Sleep Disorders:

There is insufficient information concerning effectiveness to support use of oral or sublingual L-theanine for the treatment of sleep disorders based on the populations that were discussed in articles submitted by the nominator and identified in databases that were consulted. The study that discussed L-theanine for sleep disorders in children was limited in its generalizability, lack of long-term exposure for what can be a chronic condition, and it was unclear if the study participants had a primary sleep disorder. The two studies in which L-theanine was given to adults for sleep disorders were limited by small sample sizes, lack of objective sleep measures, use of concomitant medications, and lack of clarity about whether the participants had primary sleep disorders. The databases that were consulted in the preparation of this section did not include studies in which subjects received L-theanine via the topical, IM, or SC ROA and effectiveness of administration via these ROAs in unknown. Professional society guidelines for both adults and children with primary sleep disorders do not discuss the use of L-theanine for sleep disorders. Some of the primary sleep disorders can be serious conditions and there are FDA-approved and OTC monograph therapies with established efficacy for treating sleep disorders.

[37] https://www.accessdata.fda.gov/drugsatfda_docs/omuf/OTCMonograph_M010-NighttimeSleepAidDrugProductsforOTCHumanUse_09202021.pdf. Accessed 2/23/2024.

*2. **Anxiety Disorders***

L-theanine was nominated for the uses "anxiety, relaxation, calming". Relaxation and calming are not medical disorders, but FDA will consider these uses as part of the following discussion of anxiety disorders. Anxiety disorders include disorders that share features of excessive fear and anxiety. Fear is the emotional response to real or perceived imminent threat. Anxiety is anticipation of future threat. Anxiety disorders differ from one another in the types of objects or situations that induce fear, anxiety, or avoidance behavior. Anxiety disorders can be comorbid with each other and may be comorbid with other psychiatric conditions such as major depressive disorder (MDD), obsessive compulsive disorder (OCD), or schizophrenia. Anxiety disorders differ from developmentally normative fear or anxiety by being excessive or persisting beyond developmentally appropriate periods. They differ from transient fear or anxiety by being persistent and typically last six months or more. The fear and anxiety experienced in anxiety disorders cause clinically significant distress or impairment in social, academic, occupational, or other important areas of functioning. The anxiety disorders, with a brief definition of each, are listed in Table 3 below (DSM-5-TR).

**Table 3. Anxiety Disorders Summary.**

| Anxiety Disorder | Definition |
|---|---|
| Separation Anxiety Disorder | Inappropriate and excessive fear or anxiety concerning separation from those to whom the individual is attached |
| Selective Mutism (SM) | Consistent failure to speak in specific social situations in which there is an expectation for speaking despite speaking in other situations |
| Specific Phobia (SP) | Fear or anxiety about a specific object or situation |
| Social Anxiety Disorder (SAD) | Fear or anxiety about one or more social situations in which the individual is exposed to possible scrutiny by others |
| Panic Disorder (PD) | Recurrent unexpected panic attacks |
| Agoraphobia | Fear or anxiety about being in certain public places such as in crowds or on public transportation |
| Generalized Anxiety Disorder (GAD) | Excessive anxiety and worry occurring more days than not for at least six months about a number of events or activities |
| Substance/Medication-Induced Anxiety Disorder | Panic attacks or anxiety due to use of a particular medication or substance |
| Anxiety Disorder Due to Another Medical Condition | Panic attacks or anxiety due to a specific medical condition |

Treatment goals are to decrease anxiety symptoms and to improve functioning. FDA-approved drug products, such as those indicated for GAD, PD, or SAD, evaluated endpoints such as panic attack frequency, and results of disorder specific rating scales such as the Hamilton Rating Scale

for Anxiety (HAM-A)[38] or the Liebowitz Social Anxiety Scale (LSAS)[39] to establish efficacy in confirmatory clinical trials.

Professional Society Guidelines

Practice guidelines published by the American Psychiatric Association and the American Academy of Child and Adolescent Psychiatry do not discuss the use of L-theanine for the treatment of anxiety disorders (Stein et al. 2009, Walter et al. 2020).

a. Reports of trials, clinical evidence, and anecdotal reports of effectiveness, or lack of effectiveness, of the bulk drug substance

Sarris et al. 2019:

This phase II, randomized, double-blind, placebo controlled, multi-center, 8-week pilot study enrolled 46 adults with GAD whose diagnoses were confirmed through interview and the HAM-A and who were non-responsive to their current antidepressant. The study aimed to evaluate adjunctive L-theanine in the treatment of GAD, and changes in subject reported insomnia severity. In addition to their current medications, study subjects received L-theanine 450 mg per day (given as one 225 mg capsule twice per day) or placebo matched for appearance, taste, and scent for the first four weeks of the study. Participants who did not achieve a ≥35% reduction in their baseline HAM-A score at Week-4 were titrated to two capsules, twice per day (900 mg L-theanine per day, or matching placebo) for the remaining four weeks of the treatment intervention phase. 72.7% of subjects in the L-theanine group and 8% of the study subjects in the placebo group received psychotherapy during the trial.

There were two primary outcome measures: HAM-A for the anxiety outcome (Hamilton, 1959), and the Insomnia Severity Index (ISI) for the insomnia outcome (Morin et al. 2011). The authors report that for both anxiety and insomnia outcomes, no difference between L-theanine and placebo groups was observed.

**Table 4. Mean baseline scores and change for each measure (Sarris et al. 2019).**

| Measure | Baseline, mean (SD) | | End point (week 8), mean (95% CI)* | | Statistic[1] |
|---|---|---|---|---|---|
| | Placebo | Active | Placebo | Active | |
| HAMA | 20.5 (4.98) | 21.9 (4.01) | 14.3 (11.6, 16.9) | 15.5 (12.9, 18.1) | $F(1,162) = 0.782$, $p = 0.38$ |
| MADRS | 11.9 (3.86) | 12.9 (2.85) | 9.17 (6.86, 11.5) | 11.3 (9.08, 13.5) | $F(1,162) = 0.305$, $p = 0.58$ |
| PSWQ | 62.8 (12.2) | 63.0 (10.5) | 57.6 (52.4, 62.8) | 58.2 (52.9, 63.5) | $F(1,152) = .010$, $p = 0.92$ |
| BAI | 20.3 (9.11) | 25.3 (9.58) | 10.9 (7.17, 14.6) | 12.6 (8.93, 16.2) | $F(1,153) = 0.815$, $p = 0.37$ |
| ISI | 10.9 (7.12) | 11.7 (6.05) | 10.6 (7.66, 13.5) | 9.72 (6.79, 12.6) | $F(1,47) = 0.856$, $p = 0.35$ |

HAMA – Hamilton Anxiety Rating Scale; MADRS – Montgomery-Asberg Depression Rating Scale; PSWQ – Penn State Worry Questionnaire; BAI – Beck Anxiety Inventory; ISI – Insomnia Severity Index; *Estimated marginal means derived from LMM; [1]Group × Time interaction effect from linear mixed effects model.

[38] The scale consists of 14 items, each defined by a series of symptoms, and measures both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety) (Hamilton 1959).
[39] Measure of social anxiety symptom severity and treatment outcome. The LSAS comprises 24 social situations that are each rated for level of fear and avoidance. The original scale was developed as a clinician administered measure, although a self-report version has also been validated (Beard et al. 2011).

Rizzo et al. 2022:
This open-label study evaluated effectiveness of supplementation of both L-theanine and vitamin B6 in reducing tics in 34 children aged 4-17 years with Tourette Syndrome or chronic tic disorder associated with anxiety symptoms. Subjects were randomized to receive either psychoeducation or to receive L-theanine (200 mg/day) and vitamin B6 (2.8 mg/day) daily for 2 months. All subjects were without other medication during the study.

Treatment effectiveness was measured by changes in symptom severity as evaluated by improvement in two questionnaires. The authors assessed motor and phonic tic severity using clinician rated scales (Yale Global Tic Severity Scale: YGTSS). All participants completed the Multidimensional Anxiety Scale for Children (MASC)[40], a self-report scale for anxiety in children aged 8–18 years. Those children who showed a reduction of at least 30% in YGTSS and MASC scores were considered "responders." Although there were improvements in mean YGTSS in the L-theanine + B6 group compared to psychoeducational alone intervention, there was no difference in mean MASC scores between treatment groups at two months. A limited number of subjects (n=7/17) who received L-theanine and vitamin B6 were considered "responders" on the MASC. Because study subjects received a combination of L-theanine and vitamin B6, we are unable to determine the individual contribution of each substance to reducing tics and anxiety symptoms in children with chronic tic disorders. It is unclear whether study subjects had received previous care or intervention for their tic disorders or anxiety symptoms. It is unclear whether the results of this study would be generalizable to a population of children with primary anxiety disorders as it is unknown if any study participants had a primary anxiety disorder and this study focused on anxiety symptoms in children with tic disorders. The open-label design and small sample size were also limitations of this study.

Ross et al. 2021:
In this case report of a 26-year-old woman with Post Traumatic Stress Disorder (PTSD), and Bipolar II disorder with generalized anxiety, the subject received thirteen medications and dietary supplements including L-theanine, which she took for three months. The subject reported improvement in multiple symptoms, including mood and anxiety. However, due to the number of interventions the subject received in addition to L-theanine, it is difficult to determine the role that individual therapies played in the improvements noted by the subject. Additionally, objective measurements such as validated symptom questionnaires were not used. Because this was a case report involving a single subject, the results would not be generalizable to a larger population of patients with primary anxiety disorders.

In two studies (Kardashev et al. 2018 and Ritsner et al. 2010), adult subjects with schizophrenia or schizoaffective disorder and symptoms of anxiety received L-theanine as an adjunct to their current medications. Limitations of these studies included the number of concomitant medications subjects received in addition to L-theanine. These medications included a variety of first-generation and second-generation antipsychotics, anticholinergics, and benzodiazepines. The doses and duration of treatment with these concomitant medicines were not discussed. In

[40] The MASC is a standardized, 39-item measure of anxiety, through a total score and four empirically derived factor index scores: Social Anxiety, Separation Anxiety, Harm Avoidance, and Physical Symptoms. In patients below eight years of age, the authors also administered the Child Behavior Checklist (CBCL), analyzing the raw score of the areas anxious/depressed.

one study, subjects also received pregnenolone along with L-theanine as the treatment intervention. The use of many concomitant medications makes it difficult to know the effect of L-theanine alone. Additionally, it is unclear whether the findings of these studies in regard to anxiety symptom outcomes can be generalized to patients with primary anxiety disorders alone as the presence of a comorbid psychiatric condition, such as schizophrenia, may affect anxiety symptom outcomes.

In an open-label study by Hidese et al. 2017, 20 adults with major depressive disorder received 250 mg per day of L-theanine orally for eight weeks. Anxiety symptoms were measured using the State-Trait Anxiety Inventory (STAI) and sleep quality was measured using the subjective sleep quality scale PSQI. Twelve subjects were treated with antidepressant medication and the authors report that the medication was unchanged during the intervention period. The authors do not discuss which antidepressants were used, how long the subjects had been taking these medications, or what the response to these medications was prior to enrollment in the study period. Although the authors report improvement in anxiety symptoms and sleep quality following administration of L-theanine, the design of this study is limited due to lack of blinding, lack of placebo control, and use of concomitant medications in some subjects during the intervention that confounds interpretation of the intervention. Although the subjects rated their sleep quality on a questionnaire, no additional objective measures of sleep were used such as polysomnogram or actigraph. The authors did not discuss the duration of anxiety or sleep symptoms prior to enrollment in the study, nor did they discuss previous interventions for these symptoms. It is unclear whether the findings regarding anxiety symptoms can be generalized to patients with primary anxiety disorders alone as the presence of a comorbid psychiatric condition, such as major depressive disorder, may affect anxiety symptom outcomes.

b. Whether the product compounded with this bulk drug substance is intended to be used in a serious or life-threatening disease

Anxiety disorders can be serious or life-threatening diseases. They have been associated with suicidal ideation and attempts. Anxiety disorders can be associated with high levels of social, occupational, and physical disability; and considerable economic costs (DSM-5-TR).

c. Therapies that have been used for the condition(s) under consideration

There are FDA-approved drug products that treat the same medical condition as that proposed for the L-theanine compounded drug products.[41] Table 5 below summarizes the available FDA-approved drug products for anxiety disorders.

The American Academy of Child and Adolescent Psychiatry (AACAP) recommends that cognitive-behavioral therapy (CBT) or selective serotonergic reuptake inhibitors (SSRIs), be offered to patients 6 to 18 years old with social anxiety, generalized anxiety, separation anxiety, specific phobia, or panic disorder. Combination treatment (CBT and an SSRI) could be offered

[41] FDA considers the existence of FDA-approved or OTC monograph drug products to treat the same condition as that proposed for the nomination relevant to FDA's consideration of the safety criterion, to the extent there may be therapies that have been demonstrated to be safe under the conditions of use set forth in the approved labeling. See 84 FR 4696.

preferentially over CBT alone or an SSRI alone. Serotonin norepinephrine reuptake inhibitors (SNRIs) could be offered as an alternative to SSRIs (Walter et al. 2020).

For adults with panic disorder, the American Psychiatric Association (APA) states:
"The use of a selective serotonin reuptake inhibitor (SSRI), serotonin-norepinephrine reuptake inhibitor (SNRI), tricyclic antidepressant (TCA), benzodiazepine (appropriate as monotherapy only in the absence of a co-occurring mood disorder), or cognitive-behavioral therapy (CBT) as the initial treatment for panic disorder is strongly supported by demonstrated efficacy in numerous randomized controlled trials." (Stein et al. 2009).

**Table 5. Summary of FDA-approved drug products for anxiety disorders[42]**

| Class | Drug | Adult Indications | | | Pediatric Indications |
|---|---|---|---|---|---|
| | | GAD | PD | SAD | GAD |
| **SSRI** | Fluoxetine | | X | | |
| | Sertraline | | X | X | |
| | Paroxetine | X | X | X | |
| | Escitalopram | X | | | X |
| **SNRI** | Duloxetine | X | | | X |
| | Venlafaxine | X | X | X | |
| **Azapirone** | Buspirone | X | | | |
| **Benzodiazepine** | Alprazolam | X | X | | |
| | Chlordiazepoxide | X | | | |
| | Clorazepate | X | | | >9 y |
| | Diazepam* | X | | | |
| | Lorazepam | X | | | |
| | Oxazepam | X | | | |
| | Clonazepam | | X | | |
| **Antihistamine** | Hydroxyzine | X | | | |
| **Antipsychotic** | Trifluoperazine | X | | | |

*Approved for other indications in children (convulsive disorders, and spasticity caused by upper motor neuron disorders, athetosis and stiff-man syndrome)
GAD = Generalized Anxiety Disorder, PD = Panic Disorder, SAD = Social Anxiety Disorder

Anxiety Disorders Conclusions: There is insufficient information concerning effectiveness to support use of oral L-theanine for the treatment of anxiety disorders. We were only able to find data regarding administration of L-theanine via the oral route of administration. The article that discussed L-theanine for use in children with anxiety symptoms was limited by small size, concomitant interventions, and its open label design. In the one study in adults that examined the use of L-theanine for GAD, no difference between L-theanine and placebo treatments was found. In four other references in adults with symptoms of anxiety, findings of effectiveness were limited by the presence of concomitant medications and diagnoses that make it difficult to assess the effectiveness of L-theanine as an intervention. Additionally, it was unclear if the subjects in those studies had a specific anxiety disorder. All the studies were of short duration and there is

[42] Information about the drug products in this table was obtained through the labels for the individual drug products. The labels can be accessed through the following website: https://fdalabel.fda.gov/fdalabel/ui/search. Accessed 10/13/2023.

lack of information for the long-term use of L-theanine, despite it being proposed for use for a chronic disorder. Professional society guidelines do not discuss the use of L-theanine for anxiety disorders in adults or children. Anxiety disorders can be serious conditions and there are FDA-approved therapies with established efficacy for anxiety disorders.

**Overall Conclusions**: There is insufficient information concerning effectiveness to support use of oral or sublingual L-theanine for the treatment of sleep disorders or anxiety disorders. Studies for the effectiveness of L-theanine for sleep disorders were limited by lack of long-term exposure for what can be a chronic condition, small sample sizes, lack of objective sleep measures in some studies, use of concomitant medications, and lack of clarity about whether the participants had primary sleep disorders. In one study in adults that examined the use of L-theanine for GAD, no difference between L-theanine and placebo treatments was found. Other studies for the effectiveness of L-theanine for anxiety disorders were limited by the presence of concomitant medications and diagnoses, lack of clarity whether some study subjects had a specific anxiety disorder, and short study duration resulting in lack of information for the long-term use of L-theanine, despite it being proposed for use for a chronic disorder. The databases that were consulted in the preparation of this section did not include studies in which subjects received L-theanine via the topical, IM, or SC ROA and effectiveness of these ROAs is unknown. Professional society guidelines do not discuss the use of L-theanine for sleep disorders or anxiety disorders. Sleep disorder and anxiety disorders can be serious conditions and there are FDA-approved therapies with established efficacy for anxiety disorder and sleep disorders, as well as OTC monograph drug products for use as a nighttime sleep aid.

## D. Are there concerns about the safety of the substance for use in compounding?

### *1. Nonclinical Assessment*

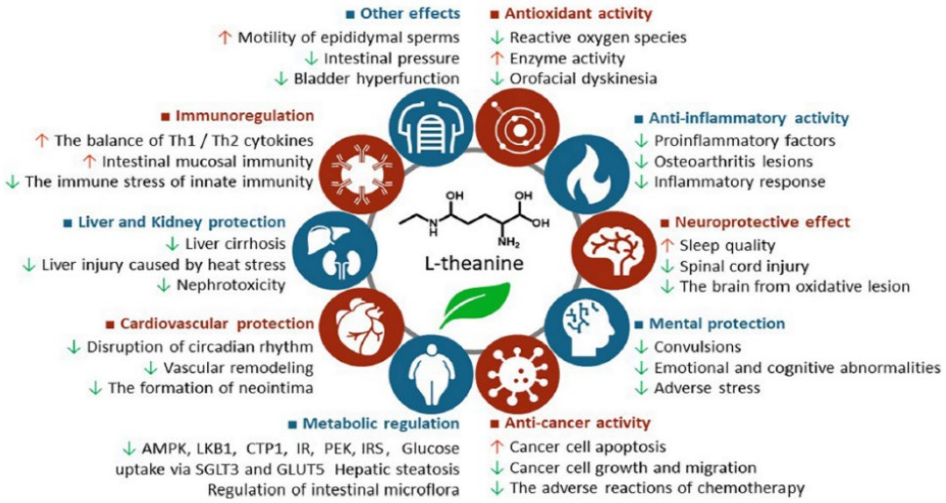
The nominator did not submit nonclinical information with the nomination.

The following databases were consulted in preparation of this section: Drugs@FDA, Embase, European Chemical Agency, Google, GRAS notice inventory, LactMed, LiverTox, National Toxicology Program website, PubChem, PubMed, Pharmapendium, USP, and Web of Science.

a. General pharmacology of the drug substance

L-theanine is a non-protein amino acid typically present in loose leaf tea from *Camellia sinensis* cultivars (Sharma et al. 2018). As illustrated in Figure 5, L-theanine exerts different pharmacological effects that are thought to contribute to health benefits commonly attributed to teas (Liu et al. 2017).

**Figure 5. Pharmacological Effects of L-theanine.**




AMPK, adenosine 50-monophosphate-activated protein kinase; CPT1, carnitine palmitoyl transferase 1; IR, insulin receptor; IRS, insulin receptor substrate; LKB1, liver kinase B1; PFK, phosphofructokinase. Figure excerpted from Liu et al. 2017.

The antioxidant properties of L-theanine have been attributed at least in part to its ability to reduce the synthesis of reactive oxygen species and enhance the expression and activity of antioxidant enzymes, including catalase, superoxide dismutase, and glutathione peroxidase 1 (Li et al. 2022). In addition, the anti-inflammatory properties of L-theanine have been associated with its ability to block the nuclear factor-κB (NF- κB) signaling pathway, thereby suppressing the expression of proinflammatory factors, including tumor necrosis factor α (TNFα), cyclooxygenase-2, prostaglandin E2, interleukin 1β, and interleukin 6 (Li et al. 2022).

In-vitro and in-vivo nonclinical studies have reported that L-theanine prevents cellular degeneration in the central nervous system, the cardiovascular system, the liver, and the kidneys. These effects of L-theanine have been largely attributed to its anti-inflammatory and antioxidant properties (Chen et al. 2022; Di et al. 2010; Kumar et al. 2023; Li et al. 2022).

Nonclinical pharmacological studies have also reported that L-theanine can prolong sleep, decrease anxiety-like behaviors,[43] reduce depression-like behaviors,[44] and improve memory in rodents. As discussed below, these effects are generally associated with L-theanine-induced increases in the levels of different neurotransmitters and in metabolic activity in the brain.

[43] In nonclinical neuropharmacological studies, the terms anxiety- and depression-like behaviors are used to refer to quantifiable species-typical neurobehaviors in animals that resemble anxiety- and depression-related states in humans and can be inhibited by treatment with an anxiolytic or an antidepressant drug, respectively. Anxiety-like behaviors in rodents include but are not restricted to: (i) decreased exploration of the open spaces of a zero maze or an elevated-plus-maze, (ii) decreased exploration of the center of a large open-field arena, and (iii) decreased exploration of a well-lit compartment in the light-dark box test. A more in-depth discussion of this topic can be found in Gencturk and Unal (2024).

[44] Depression-like behaviors in rodents include but are not restricted to: (i) increased floating time in a forced swim test, (ii) reduced preference for sucrose-containing drinking water in the sucrose preference test, and (iii) increased time to escape from a stressful stimulus in the learned helplessness task. A more in-depth discussion of this topic can be found in Gencturk and Unal (2024).

However, the cellular and molecular mechanisms by which L-theanine affects neurotransmission and metabolic activity in the brain remain poorly understood.

Zhang et al. (2021) reported that a 30-day oral treatment of 2-month-old BALB/C male mice with L-theanine (82 mg/kg/day) prolonged pentobarbital-induced sleep. The effect was accompanied by increased brain levels of the neurotransmitters known to increase sleep duration, including acetylcholine (ACh) and gamma-amino butyric acid (GABA) (Zhang et al. 2021).

Wise et al. (2012) reported that treatment of adult male ICR mice with L-theanine (8, 16, or 24 mg/kg, SC, 1x) dose dependently reduced anxiety-related behavior assessed in the elevated-plus-maze. Specifically, L-theanine significantly prolonged the time the mice spent in the open arms of the maze (Wise et al. 2012). A similar anxiolytic-like effect was observed in male Kyoto rats treated with L-theanine (0.4 mg/kg/day, intraperitoneal) for 7 days. In rats, the anxiolytic-like effect of L-theanine was accompanied by increased hippocampal activity assessed using [$^{18}$F]fluoro-deoxyglucose positron emission tomography scanning (Ogawa et al. 2018).

According to Wakabayashi et al. (2012), a three-week treatment of male mice with L-theanine (0.4, 2, or 10 mg/kg, every other day, intraperitoneal) suppressed depression-like behavior assessed in the forced swim test (FST). Specifically, compared to vehicle-treated mice, L-theanine-treated mice spent shorter time floating in the FST (Wakabayashi et al. 2012). The authors suggested that increased levels of brain-derived neurotrophic factor (BDNF) in the hippocampus may contribute at least in part to the antidepressant-like effects of L-theanine (Wakabayashi et al. 2012).

The memory-enhancing effects of L-theanine were reported in a study conducted in the APP/PS1 mouse model of Alzheimer's disease (AD) (Zhu et al. 2018). In this study, APP/PS1 mice and wildtype mice were treated for 15 days with L-theanine in drinking water (0.1 mg/mL or 0.4 mg/mL), and their cognitive behavior was compared to that of untreated mice in a fear conditioning paradigm. As expected, memory retention was impaired in untreated AD mice compared to untreated wildtype mice. L-theanine had no effect on memory retention in wildtype mice. However, the higher dose of L-theanine rescued the memory deficits presented by AD mice such that their memory retention was comparable to that of untreated wildtype mice. The authors proposed that the nootropic properties of L-theanine may be due to the improvement of synaptic plasticity in the hippocampus via a protein kinase A-dependent mechanism (Zhu et al. 2018).

b. Pharmacokinetics/Toxicokinetics (TK)

L-theanine is quickly absorbed following its oral administration to rats, and its plasma concentrations peak in approximately 30 minutes after oral dosing (Sato et al. 2021). An in-vitro study using inverted sacs prepared from the guinea pig ileum suggested that intestinal absorption of L-theanine is mediated by a sodium-coupled co-transporter in the intestinal brush border membrane (Kitaoka et al. 1996).

L-theanine distributes well to all tissues, including the brain, the liver, and the kidney (Terashima et al. 1999; Zhu et al. 2022). Following its oral administration to fasted rats, L-theanine is metabolized to glutamic acid and ethylamine, which are eliminated in urine (Unno et al. 1999).

Based on an in-vitro analysis of a rat kidney homogenate incubated with L-theanine, it appears that the hydrolysis of L-theanine into glutamic acid and ethylamine may occur in the kidneys (Unno et al. 1999).

Age and health status appear to affect the pharmacokinetics of L-theanine. Specifically, absorption of orally administered L-theanine was found to be higher in juvenile than in adult rats. In addition, oral absorption of L-theanine was higher in rats subjected to chronic unpredictable mild stress (a model of depression) than in normal rats (Zhu et al. 2022).

At the time of this evaluation, FDA did not identify nonclinical studies that assessed the pharmacokinetic profile of L-theanine delivered via the sublingual, topical, subcutaneous, or intramuscular routes of administration.

c. Acute toxicity[45]

L-theanine is generally well-tolerated, and, in rats, its oral median lethal dose (LD50) is greater than 5,000 mg/kg (Borzelleca et al. 2006).

At the time of this evaluation, FDA did not identify nonclinical studies that assessed the acute toxicity of L-theanine delivered via the sublingual, topical, subcutaneous, or intramuscular routes of administration.

d. Repeat-dose toxicity[46]

In a repeat-dose toxicity study compliant with good laboratory principles, adult male and female Sprague-Dawley rats were fed a diet containing L-theanine concentrations appropriate to deliver the oral doses of 0, 1500, 3000, or 4000 mg/kg/day for 13 weeks (Borzelleca et al. 2006). There were no treatment-related adverse effects on behavior, morbidity, mortality, clinical chemistry, hematology, or urinalysis. There were also no treatment-related adverse effects on absolute or relative organ weights or on macroscopic and microscopic histopathology of organs. The slightly reduced food consumption and body weight gain presented by L-theanine-treated rats were considered non-adverse. The authors reported that the oral no-observed adverse effect level (NOAEL) for L-theanine in rats in this study was 4,000 mg/kg/day (the highest tested dose). Based on body surface area, the oral NOAEL in rats translates into a human equivalent dose of 640 mg/kg, which provides safety margins of 96.8X and 48.8X for the highest oral dose of L-theanine (400 mg) commonly used in clinical studies in adult and pediatric populations, respectively (see Sections C and D.2 and Appendix 2, Tables E and F).

[45] Acute toxicity refers to adverse effects observed following administration of a single dose of a substance, or multiple doses given within a short period (approximately 24 hours). For more information on general approaches for acute toxicity studies, please refer to FDA's guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (January 2010), available at https://www.fda.gov/media/71542/download.

[46] Repeat-dose toxicity studies consist of in-vivo animal studies that seek to evaluate the toxicity of the test substance when it is repetitively administered daily for an extended period. For more information on general approaches for repeat-dose toxicity studies, please refer to FDA's guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (January 2010), available at https://www.fda.gov/media/71542/download.

At the time of this evaluation, FDA did not identify nonclinical repeat-dose toxicity studies with L-theanine delivered via the sublingual, topical, subcutaneous, or intramuscular routes of administration.

e. Genotoxicity[47]

L-theanine did not induce mutagenicity in in-vitro reverse mutation assays with Salmonella typhimurium, with and without metabolic activation (Ames tests with L-theanine concentrations ≤20,000 µg/plate), DNA-repair assays with Bacillus subtilis, and chromosomal aberration tests with mammalian cells in culture (Ishidate et al. 1984).

f. Developmental and reproductive toxicity[48]

At the time of this evaluation, FDA did not identify nonclinical developmental and reproductive toxicity studies with L-theanine.

g. Carcinogenicity[49]

Fujii and Inai (2008) assessed the incidence of tumors in a study of male and female B6C3F1 mice that were treated with L-theanine (0, 0.11, or 0.22 mg/kg) delivered in diet for 78 weeks (n = 50/sex/dose). B6C3F1 mice are known to have a high frequency of spontaneous tumors and are commonly used in studies for hazard identification of potential tumorigenic chemicals (Hoenerhoff et al. 2009).

Fujii and Inai (2008) reported no significant effect of the L-theanine treatment on weight gain or survival of mice. However, they reported that L-theanine reduced the number of male mice that developed tumors. At the end of the 78-week treatment with vehicle, 0.11 mg/kg L-theanine, and 0.22 mg/kg L-theanine, the percentages of mice that had tumors were 25%, 10%, and 9%,

[47] The genotoxicity assessment battery usually consists of a gene mutagenicity assay (for single dose trials) and a variety of clastogenicity/genotoxicity assays. To support multiple dose administration in humans, additional genotoxicity testing assessment is usually conducted to detect chromosomal damage in mammalian systems. For more information on general approaches for genotoxicity studies, please refer to FDA's guidance for industry *S2(R1) Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use* (June 2012), available at https://www.fda.gov/media/71980/download.

[48] Developmental and reproductive toxicity studies are usually designed to assess the potential adverse effects of a substance within a complete reproductive cycle, from conception to reproductive capacity in subsequent generations, and to identify the potential effects of a substance on pre-, peri-, and postnatal development. *Developmental toxicity* or *teratogenicity* refers to adverse effects (can include embryo-fetal mortality, structural abnormalities, functional impairment, or alterations to growth) and can occur in pups either as a result of the exposure of their parents to the substance, prior to the pups' birth, or by direct exposure of the pups to the substance after birth. For more information on general approaches for reproductive and developmental toxicity studies, please refer to FDA's guidance for industry *S5(R3) Detection of Reproductive and Developmental Toxicity for Human Pharmaceuticals* (May 2021), available at https://www.fda.gov/media/148475/download.

[49] Studies that assess cancer risk in animals are used as predictive tools to evaluate the potential for drugs to cause tumors when used by humans on a chronic basis. Carcinogenicity studies are conducted if the clinical use is expected to be continuous for a minimum of 6 months of life, or if intermittent clinical use is expected to total 6 months or more of life. For more information on general approaches for carcinogenicity studies, please refer to FDA's guidance for industry *S1B Testing for Carcinogenicity of Pharmaceuticals* (July 1997), available at https://www.fda.gov/media/71935/download.

respectively. These results suggested that L-theanine might have antitumorigenic properties (Fujii and Inai 2008). In support of a potential antitumorigenic property of L-theanine, there is a report that L-theanine can directly suppress invasion of the rat ascites hepatoma cell line AH109A across rat mesentery-derived mesothelial-cell monolayers without restricting AH109A cell proliferation (Zhang et al. 2001).

The 78-week treatment duration in the in-vivo study by Fujii and Inai is generally considered insufficient for an assessment of the tumorigenic potential of chemicals in part because it covers only 58% of the lifespan of B6C3F1 mice (approximately 134 weeks). As discussed by Haseman and colleagues, rodent carcinogenicity studies that last 12 to 18 months would be equivalent to evaluating human cancer in 30- to 50-year-old subjects and would, therefore, result in markedly reduced sensitivity to detect the carcinogenic potential of an exposure (Haseman et al. 2001).

In November 2022, FDA published the guidance entitled *S1B(R1) Addendum to S1B Testing for Carcinogenicity of Pharmaceuticals*, which discusses the use of a weight-of-evidence analysis to assess the human carcinogenic potential of pharmaceuticals.[50] This analysis, which takes into account the primary and off-target mechanisms of action as well the potential genetic, hormonal, and immunomodulatory effects of the chemical in addition to its pharmacokinetic profile, is used to inform whether a long-term (2-year) carcinogenicity study would add value to human risk assessment. Such weight-of-evidence analysis is not currently available for L-theanine. In the absence of this analysis, data from a long-term (2-year) carcinogenicity study together with an additional in-vivo carcinogenicity study are used to assess the carcinogenic potential of pharmaceuticals.

At the time of this evaluation, FDA did not identify nonclinical carcinogenicity studies with L-theanine delivered via the nominated sublingual, topical, subcutaneous, or intramuscular routes of administration.

**Conclusions**: At the time of this evaluation, FDA did not identify nonclinical studies to inform the potential for oral use of L-theanine to induce developmental and reproductive toxicity. In addition, FDA did not identify nonclinical studies to inform safety considerations for the potential clinical use of L-theanine via the nominated sublingual, topical, subcutaneous, or intramuscular routes of administration.

### *2. Human Safety*

The following databases were consulted in the preparation of this section: PubMed, Embase, Cochrane Database of Systematic Reviews, FDA Adverse Event Reporting System (FAERS), the Center for Food Safety and Nutrition (CFSAN) Adverse Event Reporting System (CAERS), ClinicalTrials.gov, professional healthcare organization websites, and various online clinical references and websites.

[50] *S1B(R1) Addendum to S1B Testing for Carcinogenicity of Pharmaceuticals: Guidance for Industry* (November 2022), available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/s1br1-addendum-s1b-testing-carcinogenicity-pharmaceuticals.

a. Pharmacokinetic data

In a study by van der Pijl et al. (2010), 15 healthy males received oral L-theanine as three separate interventions ($I^a$, $I^b$, and $I^c$) in doses of 25, 50, and 100 mg dissolved in a 314 g cup of hot water.[51] The pharmacokinetic findings were summarized in Table 6.

**Table 6.** Pharmacokinetic Findings for L-theanine.

| Intervention[c] | Parameter[b] | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Dose [mg] | $t_{½,a}$ [min] | $t_{max}$ [min] | $C_{max,70}$ [mg/L] | $t_{½,e}$ [min] | $AUC_{70}^{0\rightarrow\infty}$ [min·g/L] | $Cl/F_{abs}$ [L/min] | $V_{hyp}/F_{abs}$ [L] |
| $I^a$ | 24.9 ± 1.7 | 14 ± 10 | 46 ± 14 | 1.06 ± 0.22 | 67 ± 18 | 0.15 ± 0.03 | 0.20 ± 0.04 | 18 ± 3 |
| $I^b$ | 49.9 ± 1.6 | 10 ± 4 | 43 ± 9 | 2.22 ± 0.45 | 64 ± 9 | 0.28 ± 0.05 | 0.21 ± 0.03 | 19 ± 3 |
| $I^c$ | 98.6 ± 1.8 | 9 ± 4 | 41 ± 9 | 4.43 ± 0.70 | 66 ± 8 | 0.58 ± 0.10 | 0.20 ± 0.05 | 19 ± 3 |
| II | 23.1 ± 1.2 | 21 ± 10 | 55 ± 13 | 0.97 ± 0.18 | 55 ± 14 | 0.14 ± 0.02 | 0.20 ± 0.05 | 15 ± 3 |
| III | 45.2 ± 2.2 | 14 ± 7 | 51 ± 11 | 1.94 ± 0.32 | 70 ± 17 | 0.28 ± 0.05 | 0.19 ± 0.04 | 18 ± 5 |

[a] Healthy young males received three types of L-theanine-containing beverages: pure L-theanine dissolved in an aqueous solution, black tea, L-theanine-enriched black tea. A 1-compartment model with first-order input and output and lag time was used to assess pharmacokinetic parameters. Lag time across all interventions was about 8–10 min. Values are means ± SD, $n = 15$ (Intervention $I^a$, $I^b$, and $I^c$: $n = 14$).

[b] $t_{½,a}$, absorption half-life time; $t_{max}$, time of maximum plasma concentration; $C_{max,70}$, maximum plasma concentration corrected to a body weight of 70 kg; $t_{½,e}$, elimination half-life time; $AUC_{70}^{0\rightarrow\infty}$, area under the plasma concentration–time curve from $t = 0$ to $\infty$ min corrected to a body weight of 70 kg; $Cl/F_{abs}$, clearance over absolute bioavailability; $V_{hyp}/F_{abs}$, hypothetical distribution volume over absolute bioavailability.

[c] Hot water (314 g) to which either 25 mg ($I^a$), or 50 mg ($I^b$), or 100 mg pure L-theanine was added ($I^c$), a cup of black tea of 314 g, naturally containing about 25 mg L-theanine, to which either 0 (II) or 25 mg (III) tea-derived L-theanine was added. The time tea was administered was defined as $t = 0$ min.

L-theanine was absorbed quickly. For all interventions, the lag time was approximately 10 minutes and half-lives of absorption and elimination were approximately 15 and 65 minutes, respectively. After approximately 50 minutes, maximum plasma concentrations of between 1.0 and 4.4 mg/L were achieved. Maximum plasma concentration and area under the plasma-concentration–time curve (AUC) was dose proportional.

In a study by Scheid et al. (2012), twelve healthy adult subjects ingested 100 mg L-theanine via capsule (Suntheanine purchased from Taiyo Europe). Three participants also received 50 and 200 mg L-theanine via capsules. The maximum plasma concentration of L-theanine occurred 0.8 hours after intake of 100 mg L-theanine via capsules (24.3 ± 5.7 mmol/L). The AUC of L-theanine in plasma increased dose dependently after intake of 50, 100, and 200 mg L-theanine via capsules. L-theanine is metabolized to ethylamine and glutamic acid. Ethylamine and glutamic acid increased in plasma and were excreted by urine after intake of L-theanine. A minor part of L-theanine is retained in erythrocytes.

We were not able to find pharmacokinetic data for children. We were not able to find pharmacokinetic data for sublingual, topical, subcutaneous, or intramuscular routes of administration in humans.

[51] Volunteers received 25–100 mg of L-theanine from one of three sources: pure L-theanine (Suntheanine, Taiyo Kagaku, Yokkaichi, Japan; 101 w/w% pure), commercial Lipton Yellow label (2 g tea leaves per tea bag, Lipton US, Englewood Cliffs, NJ, USA), and tea-derived L-theanine (L-theanine purified from green tea, Taiyo Kagaku, Yokkaichi, Japan, 68.7 w/w % pure).

b. Reported adverse reactions (FAERS and CAERS)

The Office of Surveillance and Epidemiology conducted a search of the FAERS database for reports of adverse events (AEs) for L-theanine through September 8, 2023. The search retrieved eleven reports, of which eight were excluded due to insufficient information or duplicate cases.[52] There were three cases from FAERS associated with L-theanine, presumed to be taken orally as dietary supplements. No cases reported use of compounded L-theanine. Various AEs were reported such as diabetic ketoacidosis, balance disorder, and feeling abnormal; however, the assessment of these cases was very limited because they were confounded by other products associated with the AE, the product contained multiple other ingredients, or the case lacked adequate details.

CFSAN collects reports of AEs involving food, cosmetics, and dietary supplements in the CAERS database. A search of CAERS was conducted for AEs associated with L-theanine from 1/1/2004 through 8/17/2023 and retrieved 272 cases.

Four cases[53] listed L-theanine as the only active ingredient in the suspect product. Two of these four cases reported taking other medications so the contribution of L-theanine alone is unclear. AEs reported were allergic type reaction, increased anxiety and attention disturbance, and nausea and diarrhea.

The rest of the reports described AEs associated with products that contained multiple ingredients, and in some cases, there were reports of using other medications or substances. Although some of the reported AEs were serious[54] and included four deaths[55], it was not possible to determine whether the AE was attributable to L-theanine because of the considerable number of other ingredients in the product and/or due to the use of concomitant medications. When a person receives multiple medications or when a medication or supplement contains multiple active ingredients, it is not always possible to conclude which medication or ingredient may be causing AEs. Also, there is not always enough information provided in the case history (such as medical history or underlying medical conditions) to determine what might have caused a specific AE. Details of the eight CAERS cases discussed above (four cases involving L-theanine as a single API and four cases in which patient deaths were reported) are listed in Table D in Appendix 2.

c. Clinical studies assessing safety

We identified a total of 36 published studies assessing the use of L-theanine in healthy subjects and different patient populations. We grouped these studies into three groups: healthy subjects, adult patients with medical conditions, and pediatric patients with medical conditions.

[52] It is important to note that FAERS data have limitations. First, there is no certainty that the reported adverse event was due to the suspect product. FDA does not require that a causal relationship between a product and event be proven, and the report may not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that may potentially occur with a product, especially for compounded products. Considering these limitations, FDA cannot make definitive conclusions regarding the safety of L-theanine.
[53] Cases Report IDs: 183510, 207291, 212952, 213231.
[54] Cases Report IDs: 185487, 187923, 201833, 2020-cfs-006241.
[55] Reported death causes: intracranial hemorrhage, malignant hypertension, cardiac arrhythmia, and heart attack.

In 19 studies involving 554 healthy adults who received oral L-theanine, study subjects were exposed to 50-600 mg/day over a time period of 1 day to 6 weeks. In six of these studies, the authors reported that they did not observe AEs.[56] In the remaining thirteen studies, AEs were neither reported nor discussed.[57] Further details of these studies are in Table E in Appendix 2.

In 13 studies involving 732 adults with anxiety disorders, obsessive-compulsive disorder (OCD), schizophrenia, sleep difficulties, major depressive disorder, cognitive impairment, or cancer, study subjects were exposed to 50-900 mg/day of oral L-theanine. Duration of treatment ranged from 35 days to 20 weeks. In four of the studies, no AEs were reported by study participants.[58] In four of the studies, AEs were neither reported nor discussed.[59] Five of the studies reported AEs.[60] Gastrointestinal disturbances were reported in all five studies.[61] Sleep disturbances were reported in three studies.[62] Reported AEs from the five studies included: agitation, sedation, increased duration of sleep, vivid dreams, appetite loss, nausea, vomiting, diarrhea, constipation, reflux, headache, tachycardia, fatigue, neutropenia, elevated C-reactive protein, and exacerbations in OCD requiring in-patient admission.[63] In these studies, it is not known whether the reported AEs were due to L-theanine or due to other concomitant medications.

In four studies involving 234 children with ADHD, sleep difficulties, anxiety disorders, tic disorders, or other behavioral diagnoses, study subjects were exposed to between 100-400 mg/day or 2.5 mg/kg of oral L-theanine. In one of the four studies, exposure was via the sublingual ROA at a dose of 100 mg/day of L-theanine. Among all the studies, subjects were exposed to L-theanine over 4 days to 8 weeks. No AEs were reported in three of the four studies.[64]

In the study that reported an AE, the authors evaluated sleep quality in boys with ADHD who received either placebo or 400 mg of L-theanine daily. One adverse event was reported in the L-theanine group that occurred four days after drug initiation. The child developed a new subtle facial tic; however, he had a history of having a variety of tics in the past including facial tics. His study participation ended, and the new tic was reported to have ceased. No other adverse events were reported (Lyon et al. 2011).

All of the human study subjects received oral or sublingual L-theanine. Details of the four studies that involved children and the fourteen studies that involved adults with underlying sleep disorders and other medical conditions are included in Table F listed in Appendix 2. The

[56] Juszkiewicz et al. 2019; Dassanayake et al. 2022; Yuan et al. 2021; Kahathaduwa et al. 2017; Lu et al. 2004.
[57] Dodd et al. 2015; Kahathaduwa et al. 2018; Kelly et al. 2008; Gomez-Ramirez et al. 2009; Giles et al. 2017; Foxe et al. 2012; Giesbrecht et al. 2010; Furushima et al. 2022; Ota et al. 2014; Owen et al. 2008; Nobre et al. 2008; Baba et al. 2021; Yoto et al. 2012.
[58] Thiagarajah et al. 2022; Ross et al. 2021; Kardashev et al. 2018; Ritsner et al. 2011.
[59] Ota et al. 2015; Park et al. 2011; Miodownik et al. 2011.
[60] Sarris et al. 2019; Sarris et al. 2022; Hidese et al. 2017; Tsuchiya et al. 2016; Matsumoto et al. 2011.
[61] Sarris et al. 2019; Sarris et al. 2022; Hidese et al. 2017; Tsuchiya et al. 2016; Matsumoto et al. 2011.
[62] Sarris et al. 2019; Sarris et al. 2022; Hidese et al. 2017.
[63] Sarris et al. 2019; Sarris et al. 2022; Hidese et al. 2017; Tsuchiya et al. 2016; Matsumoto et al. 2011.
[64] Rizzo et al. 2022; Kahathaduwa et al. 2020; Cross et al. 2011.

databases that were consulted in the preparation of this section did not reveal studies in which subjects received topical, IM, or SC L-theanine.

d. Therapies that have been used for the condition(s) under consideration

There are FDA-approved therapies with established efficacy for anxiety disorder and sleep disorders, as well as OTC monograph drug products for use as a nighttime sleep aid. See sections II.C.1.c and II.C.2.c for a discussion of alternative therapies for sleep disorders and anxiety disorders.

**Conclusions**: The human study subjects on which the clinical safety data are based were administered oral or sublingual L-theanine. In half of the reviewed clinical studies, adverse events were not discussed; it is unclear if there were no AEs in these studies or if AEs were not reported. In the clinical studies including FAERS and CAERS reports where AEs were discussed, it is not clear whether the AEs (including serious adverse events) reported were attributable to L-theanine or due to the concomitant medications or comorbid clinical conditions. The observed AEs from the clinical studies included motor tics, agitation, sedation, increased duration of sleep, vivid dreams, appetite loss, nausea, vomiting, diarrhea, constipation, reflux, headache, tachycardia, fatigue, neutropenia, elevated C-reactive protein, and exacerbations in OCD requiring in-patient admission. Although oral administration of L-theanine appears to be generally well tolerated, the databases that were consulted in the preparation of this section did not include studies in which subjects received L-theanine via the topical, IM, or SC ROA and safety via these ROAs is unknown. Anxiety disorders can be serious conditions and there are FDA-approved therapies to treat these conditions. Some of the primary sleep disorders can be serious conditions and there are FDA-approved and OTC monograph therapies for treating sleep disorders.

## III. CONCLUSION AND RECOMMENDATION

We have balanced the criteria described in section II above to evaluate L-theanine for the 503A Bulks List. After considering the information currently available, a balancing of the criteria ***weighs against*** L-theanine being placed on that list based on the following:

1. L-theanine is a non-proteinogenic amino acid. It is a white to off-white, odorless, crystalline powder and soluble in water. L-theanine powder is reportedly stable for 2 years at 2-8°C. Solutions in distilled water reportedly may be stored at -20°C for up to 2 months.

   There is no information in either the publicly available scientific literature or in the CoA provided by the nominator, about BDS-related impurities and endotoxin testing in the CoA, which are considered critical quality attributes for the quality control of the nominated BDS used for the proposed dosage forms. The endotoxin testing control is especially important for compounding sterile injectable dosage forms. Therefore, the nominated BDS, L-theanine, is deemed to be not well characterized from the physical and chemical characterization perspective.

2. Results of a search of publicly available literature suggest that L-theanine has been compounded in the United States and other countries as oral formulations for age-related cognitive decline, ADHD, and disordered sleep. Compounded oral formulations have been advertised for use in various conditions, including sleep disorders and managing symptoms of anxiety and stress. According to OF product reports submitted to FDA, OFs have compounded multiple ingredient injection solution drug products containing L-theanine since 2017. However, current use of L-theanine in compounding is unknown as OFs have not reported compounding drug products containing L-theanine in the last four years.

3. There is insufficient information to support the effectiveness of oral or sublingual L-theanine for the treatment of sleep disorders or anxiety disorders. Studies for the effectiveness of L-theanine were limited by small sample size, inadequate design that lack objective measures, use of concomitant medications, and were of short duration. The nominators did not submit, and FDA did not find clinical studies assessing the effectiveness of L-theanine via the topical, IM, or SC ROA. Professional society guidelines do not discuss the use of L-theanine for sleep disorders or anxiety disorders. Sleep disorder and anxiety disorders can be serious conditions and there are FDA-approved therapies with established efficacy for anxiety disorder and sleep disorders, as well as OTC monograph drug products for use as a nighttime sleep aid.

4. At the time of this evaluation, the nominators did not submit, and FDA did not identify nonclinical studies to inform the potential for oral use of L-theanine to induce developmental or reproductive toxicity. In addition, the nominators did not submit, and FDA did not identify nonclinical studies to inform safety considerations for the use of L-theanine via the nominated sublingual, topical, subcutaneous, or intramuscular route of administration.

   The human study subjects on which the clinical safety data are based were administered oral or sublingual L-theanine. Interpretation of reports of adverse events is limited by use of concomitant medications or presence of comorbid clinical conditions. Although oral administration of L-theanine appears to be generally well tolerated, the databases that were consulted in the preparation of this section did not include studies in which subjects received L-theanine via the topical, IM, or SC ROA and safety via these ROAs is unknown. Anxiety disorders and some of the primary sleep disorders can be serious conditions and there are FDA-approved therapies for treating anxiety disorder and sleep disorder and OTC monograph therapies for treating sleep disorders.

On balance, the physiochemical characterization, information on historical use, lack of evidence of effectiveness, and safety information identified for L-theanine weigh against inclusion of this substance on the 503A Bulks list. Although available data suggests that this substance has been used historically in compounding, the proposal regarding this substance is based on the lack of data related to physiochemical characterization, safety, and effectiveness. The substance is not

well characterized from the physical and chemical characterization perspective and endotoxin testing for injectable ROAs is lacking. We do not have nonclinical and clinical safety data or effectiveness data for either sleep disorders or anxiety disorders for the topical, subcutaneous, and intramuscular routes of administration. Although oral and sublingual administration of L-theanine appears to be generally well tolerated, effectiveness data for sleep disorders and anxiety disorders via these ROAs is insufficient. The lack of data discussed above, and the existence of FDA-approved drugs to treat sleep and anxiety disorders, particularly in light of these being serious conditions, weighs against L-theanine being added to the 503A Bulks List. Accordingly, we propose not adding L-theanine to the 503A Bulks List.

## IV. REFERENCES

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision, Arlington, VA, American Psychiatric Association, 2022.

Aurora, RN, DA Kristo, SR Bista, JA Rowley, RS Zak, KR Casey, CI Lamm, SL Tracy and RS Rosenberg; American Academy of Sleep Medicine. 2012, The Treatment of Restless Legs Syndrome and Periodic Limb Movement Disorder in Adults - An Update for 2012: Practice Parameters with an Evidence-Based Systematic Review and Meta-Analysis, Sleep, 35(8): 1039-1062.

Baba, Y, S Inagaki, S Nakagawa, T Kaneko, M Kobayashi and T Takihara, 2021, Effects of L-Theanine on Cognitive Function in Middle-Aged and Older Subjects: A Randomized Placebo-Controlled Study, J Med Food, 24(4):333–341.

Beard, C, BF Rodriguez, E Moitra, NJ Sibrava, A Bjornsson, RB Weisberg and MB Keller, 2011, Psychometric Properties of the Liebowitz Social Anxiety Scale (LSAS) in a Longitudinal Study of African Americans with Anxiety Disorders, J Anxiety Disord, 25(5): 722–726.

Borzelleca, JF, D Peters and W Hall, 2006, A 13-Week Dietary Toxicity and Toxicokinetic Study with L-Theanine in Rats, Food Chem Toxicol, 44(7):1158-1166.

Buckley, AW, D Hirtz, M Oskoui, MJ Armstrong, A Batra, C Bridgemohan, D Coury, G Dawson, D Donley, RL Findling, T Gaughan, D Gloss, G Gronseth, R Kessler, S Merillat, D Michelson, J Owens, T Pringsheim, L Sikich, A Stahmer, A Thurm, R Tuchman, Z Warren, A Wetherby, M Wiznitzer and S Ashwal, 2020, Practice guideline: Treatment for Insomnia and Disrupted Sleep Behavior in Children and Adolescents with Autism Spectrum Disorder, Neurology, 94:392-404.

Buysse, DJ, CF Reynolds 3rd, TH Monk, SR Berman and DJ Kupfer, 1988, The Pittsburgh Sleep Quality Index: A New Instrument for Psychiatric Practice and Research, Psych Res, 28: 193-213.

Casimir, J, Jadot J, Renard M, 1960, Séparation et Caractérisation de la N-éthyl-γ-glutamine à Partir de Xerocomus badius. Biochim Biophys Acta, 39: 462-468.

Chen, CN, MH Wang, HS Soung, SM Chen, CH Fang, YW Lin and HC Tseng, 2022, (L)-Theanine Ameliorated Rotenone-Induced Parkinsonism-Like Symptoms in Rats, Neurotox Res, 40(1):241-258.

Cross, DR, G Kellermann, LB McKenzie, KB Purvis, GJ Hill and H Huisman, 2011, A Randomized Targeted Amino Acid therapy with Behaviourally At-Risk Adopted Children, Child Care Health Dev, 37(5):671–678.

Dassanayake, T, C Kahathuduwa, V Weerasinghe, 2022, L-theanine Improves Neurophysiological Measures of Attention in a Dose-Dependent Manner: a Double-Blind, Placebo-Controlled, Crossover Study, Nutr Neurosci, 25(4): 698–708.

Di, X, J Yan, Y Zhao, J Zhang, Z Shi, Y Chang and B Zhao, 2010, L-theanine Protects the APP (Swedish Mutation) Transgenic SH-SY5Y Cell against Glutamate-Induced Excitotoxicity Via Inhibition of the NMDA Receptor Pathway, Neuroscience, 168(3):778-786.

Dodd, FL, DO Kennedy, LM Riby and CF Haskell-Ramsay, 2015, A Double-Blind, Placebo-Controlled Study Evaluating the Effects of Caffeine and L-theanine both Alone and in Combination on Cerebral Blood Flow, Cognition and Mood, Psychopharmacology (Berl), 232:2563–2576.

Ekborg-Ott, KH, Taylor A and Armstrong DW, 1997, Varietal Differences in the Total and Enantiomeric Composition of Theanine in Tea, J Agric Food Chem, 45:353–363.

Esposito, S, D Laino, R D'Alonzo, A Mencarelli, L Di Genova, A Fattorusso, A Argentiero and E Mencaroni, 2019, Pediatric Sleep Disturbances and Treatment with Melatonin, Transl Med, 17(77): 1–8.

Evans, M, AC McDonald, L Xiong, DC Crowley and N Guthrie, 2021, A Randomized, Triple-Blind, Placebo-Controlled, Crossover Study to Investigate the Efficacy of a Single Dose of AlphaWave® L-theanine on Stress in a Healthy Adult Population, Neurol Ther, 10(2):1061–1078.

Foxe, JJ, KP Morie, PJ Laud, MJ Rowson, EA De Bruin and SP Kelly, 2012, Assessing the Effects of Caffeine and Theanine on the Maintenance of Vigilance During a Sustained Attention Task, Neuropharmacology, 62: 2320–2327.

Fujii, S and K Inai, 2008, Tumorigenicity Study of L-theanine Administrated Orally to Mice, Food Chem, 110(3):643–646.

Furushima, D, I Sugiyama, Y Nomura, K Unno and H Yamada. Effect of Combined Ingestion of L-Theanine and L-Arginine for Short-Term Psychological Stress in Young Adults: A Randomized Placebo-Controlled Study, J Nutr Sci Vitaminol, 68:540–546.

Gencturk, S and G Unal, 2024, Rodent Tests of Depression and Anxiety: Construct Validity and Translational Relevance, Cogn Affect Behav Neurosci, 24(2):191-224.

Giesbrecht, T, JA Rycroft, MJ Rowson and EA De Bruin, 2010, The Combination of L-theanine and Caffeine Improves Cognitive Performance and Increases Subjective Alertness, Nutr Neurosci, 13(6):283–290.

Giles, GE, CR Mahoney, TT Brunyé, HA Taylor and RB Kanarek, 2017, Caffeine and Theanine Exert Opposite Effects on Attention under Emotional Arousal, Can J Physiol Pharmacol, 95:93–100.

Gomez-Ramirez, M, SP Kelly, JL Montesi and JJ Foxe, 2009, The Effects of L-theanine on Alpha-Band Oscillatory Brain Activity During a Visuo-Spatial Attention Task, Brain Topogr (2009) 22:44–51.

Gringas P, T Nil, J Breddy, A Frydman-Marom and RL Findling, 2017, Efficacy and Safety of Pediatric Prolonged-Release Melatonin for Insomnia in Children With Autism Spectrum Disorder, J Am Acad Child Adolesc Psych, 56(11):948–957.

Gu, H, Jiang Y and Wang J, 2004, A Practical Synthesis of Ethyl L-Glutamine (L-Theanine). Org Prep Proceed Int 36:182-185.

Gu, H, Y Jiang and J Wang, 2004, A Practical Synthesis of Ethyl L-Glutamine. ChemInform 35 http://dx.doi.org/10.1002/chin.200435184

Hamaguchi, R, T Tsuchiya, G Miyata, T Sato, K Takahashi, K Miura, H Oshio, H Ohori, K Ariyoshi, S Oyamada and S Iwase, 2020, Efficacy of Oral Administration of Cystine and Theanine in Colorectal Cancer Patients Undergoing Capecitabine-based Adjuvant Chemotherapy after Surgery: A Multi-institutional, Randomized, Double-blinded, Placebo-controlled, Phase II Trial (JORTC-CAM03), Support Care Cancer, 28(8):3649–3657.

Hamilton, M, 1959, The Assessment of Anxiety States by Rating, Brit J Med Psychol, 32: 50-55.

Haseman, J, R Melnick, L Tomatis and J Huff, 2001, Carcinogenesis Bioassays: Study Duration and Biological Relevance, Food Chem Toxicol, 39(7):739-744.

Hidese, S, M Ota, C Wakabayashi, T Noda, H Ozawa, T Okubo and H Kunugi, 2017, Effects of Chronic L-theanine Administration in Patients with Major Depressive Disorder: An Open-label Study, Acta Neuropsychiatr, 29(2):72–79.

Hidese, S, S Ogawa, M Ota, I Ishida, Z Yasukawa, M Ozeki and H Kunugi, 2019, Effects of L-theanine Administration on Stress-Related Symptoms and Cognitive Functions in Healthy Adults: A Randomized Controlled Trial, Nutrients, 11(10): 2362.

Hoenerhoff, MJ, HH Hong, TV Ton, SA Lahousse and RC Sills, 2009, A Review of the Molecular Mechanisms of Chemically Induced Neoplasia in Rat and Mouse Models in National Toxicology Program Bioassays and Their Relevance to Human Cancer, Toxicol Pathol, 37(7):835-848.

Howell M, AY Avidan, N Foldvary-Schaefer, RG Malkani, EH During, JP Roland, SJ McCarter, RS Zak, G Carandang, U Kazmi and K Ramar, 2023, Management of REM Sleep Behavior Disorder: An American Academy of Sleep Medicine Clinical Practice Guideline, J Clin Sleep Med, 19(4): 759-768.

Ishidate, M, Jr., T Sofuni, K Yoshikawa, M Hayashi, T Nohmi, M Sawada and A Matsuoka, 1984, Primary Mutagenicity Screening of Food Additives Currently Used in Japan, Food Chem Toxicol, 22(8):623–636.

Ivanenko, A, A Baroni, R Gruber, S Hartselle, KP Johnson, J Owens, U Ramtekkar and C Whitmore, 2021, Sleep Disorders: Parents' Medication Guide, Am Acad Child Adol Psych, 1–14.

Juszkiewicz A, A Glapa, P Basta, E Petriczko, K Żołnowski, B Machaliński, J Trzeciak, K Łuczkowska and A Skarpańska-Stejnborn, 2019, The Effect of L-theanine Supplementation on the Immune System of Athletes Exposed to Strenuous Physical Exercise, J Int Soc Sports Nutr, 16(7):1–14.

Kahathuduwa, CN, TL Dassanayake, AMT Amarakoon and VS Weerasinghe, 2017, Acute Effects of Theanine, Caffeine and Theanine–Caffeine Combination on Attention, Nutr Neurosci, 20(6):369–377.

Kahathuduwa, CN, CS Dhanasekara, SH Chin, T Davis, VS Weerasinghe, TL Dassanayake and M Binks, 2018, L-theanine and Caffeine Improve Target-Specific Attention to Visual Stimuli by Decreasing Mind Wandering: A Human Functional Magnetic Resonance Imaging Study, Nutr Res, 49:67-78.

Kahathuduwa, CN, S Wakefield, BD West, J Blume, TL Dassanayake, VS Weerasinghe and A Mastergeorge, 2020, Effects of L-theanine-Caffeine Combination on Sustained Attention and Inhibitory Control Among Children with ADHD: a Proof-of-Concept Neuroimaging RCT, Sci Rep, 10(1):13072.

Kardashev, A, Y Ratner and MS Ritsner, 2018, Add-On Pregnenolone with L-theanine to Antipsychotic Therapy Relieves Negative and Anxiety Symptoms of Schizophrenia: An 8-Week, Randomized, Double-Blind, Placebo-Controlled Trial, Clin Schizophr Rel Psychoses, 12(1):31–41.

Kawagishi, H and Sugiyama K, 1992, Facile and Large-Scale Synthesis of L-theanine. Biosci Biotechnol Biochem 56:689.

Kelly, SP, M Gomez-Ramirez, JL Montesi and JJ Foxe, 2008, L-theanine and Caffeine in Combination Affect Human Cognition as Evidenced by Oscillatory Alpha-Band Activity and Attention Task Performance, J Nutr, 138:1572S–1577S.

Kitaoka, S, H Hayashi, H Yokogoshi and Y Suzuki, 1996, Transmural Potential Changes Associated with the in Vitro Absorption of theanine in the Guinea Pig Intestine, Biosci Biotechnol Biochem, 60(11):1768–1771.

Kumar, S, A Awasthi, K Raj and S Singh, 2023, L-theanine Attenuates LPS-Induced Motor Deficit in Experimental Rat Model of Parkinson's Disease: Emphasis on Mitochondrial Activity, Neuroinflammation, and Neurotransmitters, Psychopharmacology (Berl), 240(7):1493–1508.

Li, MY, HY Liu, DT Wu, A Kenaan, F Geng, HB Li, A Gunaratne, H Li and RY Gan, 2022, L-theanine: A Unique Functional Amino Acid in Tea (Camellia Sinensis L.) with Multiple Health Benefits and Food Applications, Front Nutr, 9:853846.

Lichtenstein, N, 1942, Preparation of c-Alkylamides of Glutamic Acid. J Am Chem Soc 64:1021–1022.

Liu, ZW, ZJ Wu, H Li, YX Wang and J Zhuang, 2017, L-theanine Content and Related Gene Expression: Novel Insights into Theanine Biosynthesis and Hydrolysis among Different Tea Plant (Camellia Sinensis L.) Tissues and Cultivars, Front Plant Sci, 8:498.

Lu, K, MA Gray, C Oliver, DT Liley, BJ Harrison, CF Bartholomeusz, KL Phan and PJ Nathan, 2004, The Acute Effects of L-theanine in Comparison with Alprazolam on Anticipatory Anxiety in Humans, Hum Psychopharmacol Clin Exp, 19:457–465.

Lyon, MR, MP Kapoor, and LR Juneja, 2011, The Effects of L-theanine (Suntheanine®) on Objective Sleep Quality in Boys with Attention Deficit Hyperactivity Disorder (ADHD): a Randomized, Double-blind, Placebo-controlled Clinical Trial, Altern Med Rev: J Clin Therap, 16(4):348–354.

Maski, K, L Trotti, S Kotagal, R Robert Auger, JA Rowley, SD Hashmi and NF Watson, 2021, Treatment of Central Disorders of Hypersomnolence: An American Academy of Sleep Medicine Clinical Practice Guideline, J Clin Sleep Med, 17(9):1881–1893.

Mason, R, 2001, 200 mg of Zen: L-theanine Boosts Alpha Waves, Promotes Alert Relaxation, Altern Complement Ther, 7(2):91-95.

Matsumoto, K, H Yamada, N Takuma, H Niino and YM Sagesaka, 2011, Effects of Green Tea Catechins and theanine on Preventing Influenza Infection Among Healthcare Workers: A Randomized Controlled Trial, BMC Complement Altern Med, 11, 15.

Miodownik, C, R Maayan, Y Ratner, V Lerner, L Pintov, M Mar, A Weizman and MS Ritsner, 2011, Serum Levels of Brain-Derived Neurotrophic Factor and Cortisol to Sulfate of Dehydroepiandrosterone Molar Ratio Associated With Clinical Response to L-theanine as Augmentation of Antipsychotic Therapy in Schizophrenia and Schizoaffective Disorder Patients, Clin Neuropharm, 34:155–160.

Miyake, K and Kakita S, 2009, A Novel Catalytic Ability of $\gamma$ -Glutamylcysteine Synthetase of Escherichia coli and Its Application in Theanine Production. Biosci Biotechnol Biochem 73:2677–2683.

Morgenthaler, TI, T Lee-Chiong, C Alessi, L Friedman, RN Aurora, B Boehlecke, T Brown, AL Chesson Jr, V Kapur, R Maganti, J Owens, J Pancer, TJ Swick, R Zak; Standards of Practice Committee of the American Academy of Sleep Medicine, 2007, Practice Parameters for the Clinical Evaluation and Treatment of Circadian Rhythm Sleep Disorders. An American Academy of Sleep Medicine report, Sleep, 30(11):1445–1459.

Morgenthaler, TI, S Kapen, T Lee-Chiong, C Alessi, B Boehlecke, T Brown, J Coleman, L Friedman, V Kapur, J Owens, J Pancer, T Swick; Standards of Practice Committee; American Academy of Sleep Medicine, 2006, Practice Parameters for the Medical Therapy of Obstructive Sleep Apnea, Sleep, 29(8):1031–1035.

Morgenthaler, TI, J Owens, C Alessi, B Boehlecke, TM Brown, J Coleman Jr, L Friedman, VK Kapur, T Lee-Chiong, J Pancer, TJ Swick; American Academy of Sleep Medicine., 2006b, Practice Parameters for Behavioral Treatment of Bedtime Problems and Night Wakings in Infants and Young Children, Sleep, 29(10):1277–1281.

Morin, C, G Belleville, L Bélanger and H Ivers, 2011, The Insomnia Severity Index: Psychometric Indicators to Detect Insomnia Cases and Evaluate Treatment Response, Sleep, 34(5):601–608.

Mu, W, Zhang T and Jiang B, 2015, An Overview of Biological Production of L-theanine. Biotechnol Adv 33:335-42.

Nandakumar, R, Yoshimune K, Wakayama M and Moriguchi M, 2003, Microbial Glutaminase: Biochemistry, Molecular Approaches and Applications in the Food Industry. J Mol Catalysis B – Enzymes 23:87–100.

Nematizadeh, M, H Ghorbanzadeh, H Moghaddam, M Shalbafan, M Boroon, A Keshavarz-Akhlaghi and Akhondzadeh S, 2023, L-theanine Combination Therapy with Fluvoxamine in Moderate-to-Severe Obsessive-Compulsive Disorder: A Placebo-Controlled, Double-Blind, Randomized Trial, Psychiatry Clin Neurosci, 77(9):478-485

Noah, L, V Morel, C Bertin, E Pouteau, N Macian, C Dualé, B Pereira and G Pickering, 2022, Effect of a Combination of Magnesium, B Vitamins, Rhodiola, and Green Tea (L-theanine) on Chronically Stressed Healthy Individuals – A Randomized, Placebo-Controlled Study, Nutrients, 14(9):1863.

Nobre, A, A Rao and G Owen, 2008, L-theanine, A Natural Constituent in Tea, and Its Effect on Mental State, Asia Pac J Clin Nutr, 17(S1):167-168.

Ogawa, S, M Ota, J Ogura, K Kato and H Kunugi, 2018, Effects of L-theanine on Anxiety-Like Behavior, Cerebrospinal Fluid Amino Acid Profile, and Hippocampal Activity in Wistar Kyoto Rats, Psychopharmacology (Berl), 235(1):37-45.

Ota, M, C Wakabayashi, J Matsuo, Y Kinoshita, H Hori, K Hattori, D Sasayama, T Teraishi, S Obu, H Ozawa and H Kunugi, 2014, Effect of L-theanine on Sensorimotor Gating in Healthy Human Subjects, Psych Clin Neurosci, 68:337–343.

Ota, M, C Wakabayashi, N Sato, H Hori, K Hattori, T Teraishi, H Ozawa, T Okubo and H Kunugi, 2015, Effect of L-theanine on Glutamatergic Function in Patients with Schizophrenia, Acta Neuropsychiatrica, 27(5) 291–296.

Owen, G, H Parnell, EA De Bruin and JA Rycroft, 2008, The Combined Effects of L-theanine and Caffeine on Cognitive Performance and Mood, Nutr Neurosci, 11(4):193–198.

Park, SK, IC Jung, WK Lee, YS Lee, HK Park, HJ Go, K Kim, NK Lim, JT Hong, SY Ly and SS Rho, 2011, A Combination of Green Tea Extract and L-theanine Improves Memory and Attention in Subjects with Mild Cognitive Impairment: A Double-blind Placebo-controlled Study, J Med Food, 14(4):334–343.

Post, R and S Kurlansik, 2012, Diagnosis and Management of Attention-Deficit/Hyperactivity Disorder in Adults, Am Fam Phys, 85(9): 891–896.

Ritsner, MS, C Miodownik, Y Ratner, T Shleifer, M Mar, L Pintov and V Lerner, 2011, L-theanine Relieves Positive, Activation, and Anxiety Symptoms in Patients with Schizophrenia and Schizoaffective Disorder: An 8-week, Randomized, Double-blind, Placebo-controlled, 2-Center Study, J Clin Psychiatry, 72(1):34–42.

Rizzo, R, A Prato, M Scerbo, F Saia, R Barone and P Curatolo, 2022, Use of Nutritional Supplements Based on L-theanine and Vitamin B6 in Children with Tourette Syndrome, with Anxiety Disorders: A Pilot Study, Nutrients, 14(4):852.

Ross, K, M VanNortwick and D Dragone, 2021, Innovative therapies for mood disorders: A case report, Explore, 17:208-212.

Sakato, Y, 1949, The Chemical Constituents of Tea: A New Amide theanine, J Agric Food Chem, 23:262–267.

Sarris, J, GJ Byrne, L Cribb, G Oliver, J Murphy, P Macdonald, S Nazareth, D Karamacoska, S Galea, A Short, C Ee, Y Birling, R Menon and CH Ng, 2019, L-theanine in the Adjunctive Treatment of Generalized Anxiety Disorder: A Double-blind, Randomised, Placebo-controlled Trial, J Psychiatr Res, 110:31–37.

Sarris, J, GJ Byrne, G Oliver, L Cribb, S Blair-West, D Castle, OM Dean, DA Camfield, V Brakoulias, C Bousman, N Dowling, C Ee, J Murphy, R Menon, M Berk, S Chamoli, M Boschen and CH Ng, 2022, Treatment of Refractory Obsessive-Compulsive Disorder with Nutraceuticals (TRON): A 20-Week, Open Label Pilot Study, CNS Spectr, 27(5): 588–597.

Sato, Y, K Yamaguchi, M Ogawa, Y Takekuma and M Sugawara, 2021, An Imaging Approach for Determining the Mechanism of Enhancement of Intestinal Absorption of an L-theanine Supplement, PLoS One, 16(6):e0253066.

Sateia, MJ, DJ Buysse, AD Krystal, DN Neubauer and JL Heald, 2017, Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline, J Clin Sleep Med, 13(2): 307–349.

Scheid, L, S Ellinger, B Alteheld, H Herholz, J Ellinger, T Henn, HP Helfrich and P Stehle, 2012, Kinetics of L-theanine Uptake and Metabolism in Healthy Participants Are Comparable after Ingestion of L-theanine via Capsules and Green Tea, J Nutr 142: 2091–2096.

Shamabadi, A, F Kafi, AM Bafrani, H Asadigandomani, AF Basti and S Akhondzadeh, 2023, L-theanine Adjunct to Sertraline for Major Depressive Disorder: A Randomized, Double-blind, Placebo-Controlled Clinical Trial, J Affect Disord, 333:38–43.

Sharma, E, R Joshi and A Gulati, 2018, L-theanine: An Astounding Sui Generis Integrant in Tea, Food Chem, 242:601–610.

Stein, MB, MK Goin, MH Pollack, P Roy-Byrne, J Sareen, NM Simon and L Campbell-Sills, 2009, Practice Guideline for the Treatment of Patients With Panic Disorder, Am Psych Assoc, 1-90.

Terashima, T, J Takido and H Yokogoshi, 1999, Time-Dependent Changes of Amino Acids in the Serum, Liver, Brain and Urine of Rats Administered with Theanine, Biosci Biotechnol Biochem, 63(4):615–618.

Thiagarajah K, H Chee, N Sit, 2022, Effect of Alpha-S1-Casein Tryptic Hydrolysate and L-theanine on Poor Sleep Quality: A Double Blind, Randomized Placebo-Controlled Crossover Trial, Nutrients 2022, 14(3):652.

Tsuchiya, T, H Honda, M Oikawa, T Kakita, A Oyama, H Oishi, K Tochikubo, T Hashimoto, S Kurihara, T Shibakusa and T Kayahara, 2016, Oral administration of the amino acids cystine and theanine attenuates the adverse events of S-1 adjuvant chemotherapy in gastrointestinal cancer patients. Int J Clin Oncol, 21(6):1085–1090.

Unno, T, Y Suzuki, T Kakuda, T Hayakawa and H Tsuge, 1999, Metabolism of Theanine, Gamma-Glutamylethylamide, in Rats, J Agric Food Chem, 47(4):1593–1596.

Van der Pijl, P, L Chen and T Mulder, 2010, Human disposition of L-theanine in tea or aqueous solution, J Funct Foods, 2:239–244.

Yan SH, Dufour JP and Meurens M, 2003, Synthesis and characterization of highly pure theanine. J Tea Sci 23:99–104.

Wakabayashi, C, T Numakawa, M Ninomiya, S Chiba and H Kunugi, 2012, Behavioral and Molecular Evidence for Psychotropic Effects in L-theanine, Psychopharmacology (Berl), 219(4):1099–1109.

Walter, HJ, OG Bukstein, AR Abright, H Keable, U Ramtekkar, J Ripperger-Suhler and C Rockhill, 2020, Clinical Practice Guideline for the Assessment and Treatment of Children and Adolescents With Anxiety Disorders, J Am Acad Child Adolesc Psychiatry, 59(10):1107–1124.

Wise, LE, ID Premaratne, TF Gamage, AH Lichtman, LD Hughes, LS Harris and MD Aceto, 2012, L-theanine Attenuates Abstinence Signs in Morphine-Dependent Rhesus Monkeys and Elicits Anxiolytic-Like Activity in Mice, Pharmacol Biochem Behav, 103(2):245–252.

Wolraich, ML, JF Hagan Jr, C Allan, E Chan, D Davison, M Earls, SW Evans, SK Flinn, T Froehlich, J Frost, JR Holbrook, CU Lehmann, HR Lessin, K Okechukwu, KL Pierce, JD Winner, W Zurhellen; Subcomittee on Children and Adolescents with Attention-Deficit/Hyperactive Disorder, 2019, Clinical Practice Guideline for the Diagnosis, Evaluation and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents, Pediatrics, 144(4):e20192528.

Yoneda, Y, K Kawada and N Kuramoto, 2020, Selective Upregulation by Theanine of Slc38a1 Expression in Neural Stem Cell for Brain Wellness, Molecules, 25(2):347.

Yoto, A, M Motoki, S Murao and H Yokogoshi, 2012, Effects of L-theanine or Caffeine Intake on Changes in Blood Pressure under Physical and Psychological Stresses, J Physiol Anthropol, 31(28):1–9.

Yuan, S, JC Brown, M Gold, E Tirrell, RN Jones and LL Carpenter, 2021, Effects of Single-Dose L-theanine on Motor Cortex Excitability, Clin Neurophysiol, 132(9):2062–2064.

Zhang, G, Y Miura and K Yagasaki, 2001, Inhibitory Effects of Theanine and Sera from Theanine-Fed Rats on Receptor-Mediated Cancer Cell Invasion beneath Mesothelial-Cell Monolayers, Cytotechnology, 36(1–3):195–200.

Zhang, F, Zheng QZ, Jiao QC, Liu JZ and Zhao GH, 2010, Enzymatic Synthesis of Theanine from Glutamic Acid γ-Methyl Ester and Ethylamine by Immobilized Escherichia coli Cells with γ -Glutamyltranspeptidase Activity, Amino Acids 39:1177–1182.

Zhang, Y, X Jia, X Chen, Y Liu, Z Zhao, J Hao, R Wu, H Feng and X Ren, 2021, L-theanine and Neumentix Mixture Improves Sleep Quality and Modulates Brain Neurotransmitter Levels in Mice, Ann Palliat Med, 10(4):4572–4581.

Zhu, G, S Yang, Z Xie and X Wan, 2018, Synaptic Modification by L-theanine, a Natural Constituent in Green Tea, Rescues the Impairment of Hippocampal Long-Term Potentiation and Memory in AD Mice, Neuropharmacology, 138:331–340.

Zhu, Y, F Wang, Y Zhao, M Yu, M Ma and Z Yu, 2022, A Sensitive HILIC/MS-MS Method for Quantification of Theanine in Rat Plasma and Tissues: Application to Preclinical Pharmacokinetic Study, J Chromatogr B Analyt Technol Biomed Life Sci, 1198:123248.

Zolovska, B and J Shatkin, 2013, Key Differences in Pediatric versus Adult Sleep, Pediatr Sleep, 2013:573–578.

# V. APPENDICES

## APPENDIX 1: ADDITIONAL SLEEP INFORMATION

**Table A. Sleep Stages**[65]

| Sleep Stage | Description |
|---|---|
| Stage 1 | This is the lightest phase of sleep and generally lasts about seven minutes. The sleeper is somewhat alert and can be woken up easily. During this stage, the heartbeat and breathing slow down while muscles begin to relax. The brain produces alpha and theta waves. |
| Stage 2 | In this stage, the brain creates brief bursts of electrical activity known as "sleep spindles" that create a distinct sawtooth pattern on recordings of brain activity. Eventually, the waves continue to slow down. Stage 2 is still considered a light phase of sleep, but the sleeper is less likely to be awakened. Heart rate and breathing slow down even more, and the body temperature drops. This stage lasts around 25 minutes. |
| Stage 3 | This stage represents the body falling into a deep sleep, where slow wave sleep occurs. The brain produces slower delta waves, and there's no eye movement or muscle activity from the sleeper. As the brain produces even more delta waves, the sleeper enters an important restorative sleep stage from which it's difficult to be awakened. This phase of deep sleep is what helps a person to feel refreshed in the morning. It's also the phase in which the body repairs muscle and tissue, encourages growth and development, and improves immune function. |
| REM Sleep | About 90 minutes after falling asleep, the body enters REM sleep, which stands for Rapid Eye Movement sleep and is named so for the way the eyes quickly move back and forth behind the eyelids. REM sleep is thought to play a role in central nervous system development in infants, which might explain why infants need more REM sleep than adults. This sleep pattern is characterized by dreaming, since the brain is very active during this stage. Physically, the body experiences faster and irregular breathing, increased heart rate, and increased blood pressure; however, the arm and leg muscles become temporarily paralyzed, stopping a person from acting out dreams. The duration of REM sleep increases with each new sleep cycle, starting at about ten minutes during the first cycle and lasting up to an hour in the final cycle. |
| Stage 4 | This is the last stage before the cycle repeats. This sleep stage is critical for learning, memory, daytime concentration, and mood. |

[65] Information about sleep stages is from the National Sleep Foundation website https://www.thensf.org/what-are-the-sleep-stages/. Accessed 10/17/2023.

**Table B. Recommended Sleep Time by Age[66]**

| Age Group | | Recommended Hours of Sleep per day |
|---|---|---|
| Newborn | 0-3 months | 14-17 hours (National Sleep Foundation)<br>No recommendation (American Academy of Sleep Medicine) |
| Infant | 4-12 months | 12-16 hours per 24 hours (including naps) |
| Toddler | 1-2 years | 11-14 hours per 24 hours (including naps) |
| Preschool | 3-5 years | 10-13 hours per 24 hours (including naps) |
| School Age | 6-12 years | 9-12 hours per 24 hours |
| Teen | 13-18 years | 8-10 hours per 24 hours |
| Adult | 18-60 years | 7 or more hours per night |
| | 61-64 years | 7-9 hours |
| | 65 years and older | 7-8 hours |

**Table C. Sleep Disorder Guidelines Summary**

| Sleep Disorder | Do practice guidelines discuss the use of L-theanine for this disorder? |
|---|---|
| Insomnia | No (Sateia et al. 2017) |
| REM Sleep Disorders | No (Howell et al. 2023) |
| Obstructive Sleep Apnea | No (Morgenthaler et al. 2006) |
| Central Disorders of Hypersomnolence | No (Maski et al. 2021) |
| Circadian Rhythm Sleep-Wake Disorders | No (Morgenthaler et al. 2007) |
| Restless Leg Syndrome | No (Aurora et al. 2012) |
| Parasomnias | No (Morgenthaler et al. 2006b, Gupta et al. 2017) |

## APPENDIX 2: ADDITIONAL SAFETY INFORMATION

**Table D. Selected CAERS Adverse Events Reports for L-theanine**

| Report ID | Event Start Date | Ingredients name | Suspect Product | AEs | Additional Information |
|---|---|---|---|---|---|
| 183510 | 2/6/2015 | L-theanine, microcrystalline cellulose, silica, suntheanine, vegetable cellulose, vegetable magnesium stearate | solgar L-theanine 150 mg vegetable capsules | swollen tongue, tongue discoloration, dyspnea, cough, burning sensation, throat irritation, | The consumer took one capsule once on 02/06/2015. All medical conditions and allergies were denied. Concomitant products were reported as fish oil, vitamin d3 and choline (dosage, frequency and duration were not |

[66] https://www.cdc.gov/sleep/about/?CDC_AAref_Val=https://www.cdc.gov/sleep/about_sleep/how_much_sleep.html. Accessed 7/10/2024.

| Report ID | Event Start Date | Ingredients name | Suspect Product | AEs | Additional Information |
|---|---|---|---|---|---|
| | | | | | provided). The consumer self-treated with Benadryl 50 mg (diphenhydramine). Within 20 minutes, the swelling and whiteness of her tongue resolved, and the coughing and difficulty breathing improved and eventually resolved. The consumer continues to have burning of her tongue and lingering tickling in her throat. The consumer continues to take 50 mg of Benadryl (diphenhydramine) once per day. She has not gone to a doctor or hospital as it has not interfered with her ability to talk, breathe, or eat. |
| 207291 | 2/4/2017 | L-theanine, microcrystalline cellulose, modified cellulose (vegetable capsule), suntheanine L-theanine | doctor's best L-theanine with suntheanine | arrhythmia, disturbance in attention, drug interaction, anxiety | Concomitant medications include SSRI and beta blocker. Relevant medical history: generalized depression, social anxiety, HBP, GERD. For several weeks the consumer used L-theanine bid or qid 150-200 mg usually with caffeine (coffee). She then experienced arrhythmia, anxiety, and loss of concentration. Symptoms seem to have resolved after stopping L-theanine for a couple of days. |
| 212952 | 6/1/2017 | unknown | L-theanine | diarrhea, nausea | The consumer reported nausea x 5 days, diarrhea x 1 day that occurred 5 |

| Report ID | Event Start Date | Ingredients name | Suspect Product | AEs | Additional Information |
|---|---|---|---|---|---|
| | | | | | days after taking Whole Foods brand L-theanine after it started smelling badly, despite refrigeration. She became less nauseous within 24 hours of stopping the product. Medical History: depression, has history of IBS and yeast infection but has been having improving GI symptoms. Has mild allergy to wheat but does not eat it. |
| 213231 | 6/4/2017 | | L-theanine | nausea, retching, diarrhea | The consumer reported nausea, diarrhea and gagging after taking Whole Foods L-theanine that smelled bad. |
| 185487 | 5/8/2013 | (seed), acerola concentrate (as malpighia glabra) (fruit), acerola fruit concentrate as malpighia glabra, acesulfame-potassium, alchemilla vulgaris extract (lady's mantle) (leaf), ammonium hydroxide, ascorbic acid, bilberry extract (as vaccinium myrtillus) (fruit), bilberry extract as vaccinium myrtillus fruit, blueberry (as vaccinium corymbosum) (fruit), blueberry (vaccinium corymbosum) fruit, caffeine anhydrous, caffeine anhydrous (137-trimethylxanthine), calcium, capsule (gelatin, caramel color, carboxymethylcellulose sodium, cayenne pepper (as capsicum annuum) (fruit), citric acid, co-enzyme q10, colors (black carrot juice & | hydroxycut max pro clinical liquid caps, hydroxycut pro clinical caplets, hydroxycut pro clinical gummies, hydroxycut hardcore rapid release capsules (dietary supplement) capsules | brain injury, leukocytosis, blood glucose decreased, ammonia increased, pulmonary oedema, mental impairment, respiratory distress, cardiac arrest, dyspnoea, vomiting, anoxia, tachycardia, transaminases increased, convulsion, hypophosphataemia, dysarthria, tachypnoea, aspartate aminotransferase increased, hypothyroidism, hypertension, brain oedema, nausea, blood thyroid stimulating hormone increased, intracranial pressure increased, oedema, pupil fixed, brain death, blood lactic acid increased, pleural effusion, unresponsive to | 31-year-old Caucasian female who was taking hydroxycut hardcore rapid release capsules, hydroxycut max pro clinical liquid-caps, hydroxycut pro clinical caplets, hydroxycut pro clinical gummies, Tylenol pm (acetaminophen with diphenhydramine), ethanol, opioids, and crystal light. Medical history included an allergy to codeine, a collapsed lung (1992), a history of over-the-counter anti-obesity drug usage, no hospitalizations except for childbirth, a miscarriage at 4 weeks (1994), a prior history of smoking, |

| Report ID | Event Start Date | Ingredients name | Suspect Product | AEs | Additional Information |
|---|---|---|---|---|---|
| | | purple berry concentrate), corn syrup, cumin extract as cuminum cyminum seed, cuminum cyminum extract (komiin) (seed), dicalcium phosphate, fd&c blue no. 1, fd&c red no, fd&c red no.40, folic acid, fractionated coconut oil (contains carnauba wax and/or beeswax), gelatin, gelatin capsule, glutathione, goji extract (as lycium barbarum) (fruit), goji extract as lycium barbarum fruit, green coffee extract (as c. canephora robusta), gummies blend, hydroxagen, hydroxypropyl cellulose, hydroxyprovia, ink shellac, iron (as ferrous gluconate dihydrate), komijn extract (as cuminum cyminum) (seed), l-alanine, l-glutamic acid Hcl l-isoleucine, l-leucine, l-methionine, l-serine, L-theanine, l-threonine, l-tyrosine, lactic acid, lady's mantle (alchemilla vulgaris) leaf extract, lady's mantle extract (as alchemilla vulgaris) (leaf), lo han fruit (concentrate), magnesium stearate, maltodextrin, max hydroxagen, max hydroxyboost, max predefine, menthe longifolia extract (wild mint) (leaf), microcrystalline cellulose, natural flavors, norepidrol, olea europaea extract (wild olive) (leaf), oleic acid, olive (olea europaea) leaf extract, | | stimuli, blood ethanol increased, body temperature decreased, dizziness, drug screen positive, respiratory alkalosis, myxoedema, metabolic acidosis, hypokalaemia, depressed level of consciousness, renal failure acute, mental disorder, death, alanine aminotransferase increased, toxicity to various agents, pneumothorax, acute hepatic failure, adverse drug reaction, blood fibrinogen increased, diastolic dysfunction, lactic acidosis, blood bilirubin increased, insomnia, pain, fatigue | irritable bowel syndrome (IBS), herpes, asthma, obesity, and no history of illicit drug use. She had a change in mental status after taking the above substances, was hospitalized, and subsequently died. |

| Report ID | Event Start Date | Ingredients name | Suspect Product | AEs | Additional Information |
|---|---|---|---|---|---|
| | | polydimethylsiloxane, polyethylene glycol (coating), polysorbate 80, pomegranate (as punica granatum) (fruit and seed), pomegranate (punica granatum), propylene glycol, proxyclene anhydranine, sesame oil, silica, silicon dioxide, stearic acid, sugar, talc (coating), titanium dioxide, titanium dioxide (coating), trans-ferulic acid, tricalcium phosphate, vitamin c (as ascorbic acid), water, wild mint extract (as mentha longifolia) (leaf), wild mint extract as mentha longifolia leaf, wild olive extract (as olea europaea) (leaf), yohimbacore robusta, yohimbe extract (as pausinystalia yohimbe) (bark) | | | |
| 187923 | 7/6/2015 | arginine inositol silicate, beta-alanine, caffeine, choline bitartrate, hydromax tm, L-theanine, rhodiola extract, yohimbe | anarchy max potency pre-workout | brain stem haemorrhage, neck pain, computerised tomogram abnormal, death, headache, unresponsive to stimuli, malignant hypertension, paralysis flaccid, miosis, hiccups, dizziness, haemorrhage intracranial, hypertensive crisis, brain death | The consumer was a 26 y/o male who was well until he took the energy booster anarachy and went to the gym. At the time of the incident, he felt a sudden, severe headache, dizziness and neck pain. He was hospitalized and was diagnosed with pontine hemorrhage most likely due to energy drink induced hypertension. At the time of the report his prognosis was poor as he was reported to likely be brain dead. Relevant medical history: allergies: penicillin smoking/alcohol status unknown, drug |

| Report ID | Event Start Date | Ingredients name | Suspect Product | AEs | Additional Information |
|---|---|---|---|---|---|
| | | | | | screen: negative, liver/kidney function: normal |
| 201833 | 6/15/2015 | beta phenylrthylamine Hcl blue sugar spheres (sugar, corn starch, & fd&c blue #1), caffeine, croscarmellose sodium, dicalcium phosphate, hordenine hcl, L-theanine, magnesium stearate, microcrystalline cellulose, pharmaceutical glaze (shellac & providone), silicon dioxide, stearic acid | fenfast 375 | death, arrhythmia | The consumer took a diet supplement to lose weight. Only one dose (2 capsules) of fenfast 375, made by intechra health, was missing from the vial on the day he died. The recommended dosage is 2 capsules twice a day. Neither the police report nor the coroner's report indicated any unusual circumstances or health conditions. Relevant medical history: no pre-existing medical conditions. The coroner's report concluded death was "natural" because there were no obvious causes identified via autopsy. |
| 2020-cfs-006241 | 5/25/2020 | caffeine anhydrous, cayenne pepper (as capsicum annuum) (fruit), fd&c blue no. 1, fd&c red no. 40, gelatin, green coffee extract (as c. canephora robusta) (seed), l-leucine, l-methionine, L-theanine, l-tyrosine, magnesium stearate, microcrystalline cellulose, silicon dioxide, titanium dioxide, trans-ferulic acid, yohimbe extract (as pausinystalia yohimbe) (bark) | hydroxycut hardcore rapid release capsules | death, myocardial infarction | A 66-year-old female was using hydroxycut hardcore rapid release capsules (dietary supplement). Concomitant medications: ProAir (albuterol sulfate), Spiriva (budesonide and formoterol fumarate dihydrate aerosol), fluticasone, spiriva (tiotropium bromide) and omeprazole. Medical history included asthma, unspecified seasonal allergies, a non-smoker, and her caffeine consumption |

| Report ID | Event Start Date | Ingredients name | Suspect Product | AEs | Additional Information |
|---|---|---|---|---|---|
| | | | | | was a coke or mountain dew (unknown how much). 1-2 months prior to death, the consumer started using hydroxycut hardcore rapid release capsules, possibly at 2 capsules a day, orally, per product directions. There were 28 capsules left in the bottle and there were 60 capsules to start. The consumer passed away. The death certificate cited the consumer died of a heart attack. The consumer's sister alleged the consumer had died due to the use of the supplement product. |

**Table E. Summary Of Adverse Events In Studies Involving Healthy Subjects Exposed To Oral L-theanine**

| Article | Population | Intervention | AE's |
|---|---|---|---|
| Hidese et al. 2019 | 30 healthy adults | L-theanine 200 mg/day for 4 weeks vs placebo | none |
| Owen et al. 2008 | 27 healthy adults | Suntheanine 100 mg/day once vs placebo | not discussed |
| Nobre et al. 2008 | 35 healthy adults (16 L-theanine, 19 control) | L-theanine 0.5 mg/kg (total 50 mg/serving) once vs water | not discussed |
| Baba et al. 2021 | 50 healthy adults (26 L-theanine, 24 placebo) | Suntheanine 100.6 mg once vs placebo | not discussed |
| Yoto et al. 2012 | 16 healthy adults | L-theanine (200 mg/day) or caffeine (100 mg) each given once vs placebo | not discussed |
| Juszkiewicz et al. 2019 | 20 healthy adult male rowers (athletes) | L-theanine 150 mg/day for 6 weeks vs placebo | none |
| Dassanyake et al. 2022 | 27 healthy adults | L-theanine 100, 200, 400 mg given once at each dose (no placebo) | none |
| Dodd et al. 2015 | 24 healthy adults | caffeine (75 mg), L-theanine (50 mg), caffeine + L-theanine each intervention given once vs placebo | not discussed |
| Yuan et al. 2021 | 10 healthy adults | L-theanine 400 mg once vs placebo | none |
| Kahathaduwa et al. 2017 | 20 healthy adult males | L-theanine (200 mg/day), caffeine (160 mg), combo, black tea each intervention given once vs placebo | none |
| Kahathaduwa et al. 2018 | 9 healthy adult males | 200 mg/day L-theanine, 160 mg caffeine, combo, each intervention was given once vs distilled water | not discussed |
| Kelly et al. 2008 | 16 healthy adults | L-theanine (100 mg/day), caffeine (50 mg), both, each intervention given once vs placebo | not discussed |
| Gomez-Ramirez et al. 2009 | 13 healthy adults | L-theanine 250 mg given once vs water | not discussed |
| Lu et al. 2004 | 16 healthy adults | L-theanine (200 mg), alprazolam 1 mg each intervention given once vs placebo | none |
| Giles et al. 2017 | 36 healthy adults | L-theanine (200 mg), caffeine (200 mg), combo, each intervention given once vs placebo | not discussed |
| Foxe et al. 2012 | 27 healthy adults | L-theanine (100 mg), caffeine, combo, each intervention given once vs placebo | not discussed |
| Geisbrecht et al. 2010 | 44 adults | oral L-theanine (97 mg) and caffeine (40 mg), each intervention given once vs placebo | not discussed |
| Furushima et al. 2022 | 120 healthy adults | L-theanine (200 mg), L-theanine + arginine (200 mg + 50 mg), each intervention given once vs placebo | not discussed |
| Ota et al. 2014 | 14 healthy adults | L-theanine 0, 200, 400, 600 mg, each subject received one of each dose | not discussed |

**Table F. Summary of Study Adverse Events for Specific Disease Conditions in Adults**

| Reference | Intervention | L-theanine Dose | Duration | Population | AEs |
|---|---|---|---|---|---|
| Thiagarajah et al. 2022 | RLX2 = alpha S1 casein tryptic hydrolysate + LT Placebo= milk powder | 50 mg/day | 4 weeks | 39 Adults (Healthy with poor sleep quality) | None reported |
| Ota et al. 2015 | LT + current medications (open label) | 250 mg/day | 8 weeks | 17 Adults with schizophrenia | Not discussed |
| Sarris et al. 2019 | LT + current medications | 450-900 mg/day | 8 weeks | 46 Adults with GAD | sleep disturbance (active=11, placebo=15), drowsiness (active=11, placebo=11), weakness/fatigue (active=9, placebo=13), irritability (active=9, placebo=11), trouble concentrating (active=7, placebo=11) and gastrointestinal discomfort (active=7, placebo= 10). No significant difference in AEs between LT and placebo groups or between LT doses |
| Sarris et al. 2022 | LT + NAC + zinc + magnesium + pyridoxal-5' phosphate + selenium + other psychiatric medications | 600 mg/day | 20 weeks | 28 Adults with treatment resistant OCD | At least 8 subjects with AEs that led to study withdrawal: agitation, sedation, nausea, tachycardia, digestive complaints, vivid dreams, fatigue, worsening physical and mental health, elevated CRP, exacerbations in OCD requiring in-patient admission. The most reported adverse events were nausea (n = 9), which was associated with vomiting in two participants, diarrhoea (n = 3), headache (n = 3), constipation (n = 3), reflux (n = 3) and gustatory disturbance (n = 3). Gastric adverse events were typically transient and resolved at subsequent visits (however two participants were withdrawn due to this reason). These adverse events often improved following advice to |

| Reference | Intervention | L-theanine Dose | Duration | Population | AEs |
|---|---|---|---|---|---|
| | | | | | consume the nutrients with food. |
| Ross et al. 2021 | LT + Lamictal + lithium + tryptophan + L-glutamine, D-phenylalanine + tyrosine + MVI + magnesium citrate + zinc + gamma-linoleic acid + glycine + Vitamin C with quercetin | 200 mg BID X 3 months, then 200 mg TID | 3 months | Adult Case report | None related to LT |
| Kardashev et al. 2018 | LT + Pregnenolone + current medications | 400 mg/day | 8 weeks | 40 Adults with schizophrenia or schizoaffective disorder | No reported differences between treatment arms |
| Ritsner et al. 2010 | LT + current medications | 400 mg/day | 8 weeks | 40/60 Adults with schizophrenia or schizoaffective disorder | No treatment related AE's in either treatment group |
| Hidese et al. 2017 | LT + current medications | 250 mg/day | 8 weeks | 20 Adults with MDD | One patient reported slight sleepiness, two patients reported increased duration of sleep of up to 2 h longer than usual, and two patients reported slightly increased dream activity. |
| Park et al. 2011 | LT + green tea extract (ingredients of GTE unknown) called LGNC-07 | 240 mg/day | 16 weeks | 91 adults with mild cognitive impairment | Not discussed |
| Miodownik et al. 2011 | LT + current medications (? Same subjects as Ritsner et al. 2010) | 400 mg/day | 8 weeks | 40 adults with schizophrenia | Not discussed |
| Hamaguchi 2019 | L-Cysteine + L-theanine + chemotherapy | 280 mg/day | 12 weeks | 100 Adults with colorectal cancer receiving capecitabine-based adjuvant chemotherapy | no significant increases in the incidence rate of AEs of grade 1 or higher, as well as grade 2 or higher, associated with the L-cystine/L-theanine group compared with the placebo group (see Table3) |
| Tsuchiya 2016 | Cysteine + theanine + chemotherapy | 280 mg/day | 35 days | Adults with gastrointestinal cancer receiving S-1 adjuvant chemotherapy | Incidence of Neutropenia, Appetite loss and nausea were higher in C/T group than in control group |

| Reference | Intervention | L-theanine Dose | Duration | Population | AEs |
|---|---|---|---|---|---|
| Matsumoto 2011 | LT + green tea catechins vs placebo | 210 mg/day | 5 months | 200 Adults | No SAE's were observed during the study. Bloating and constipation occurred in both groups and did not differ between groups. |

# L-Theanine
# Nomination

| | |
|---|---|
| **Company Name** | **Wells Pharmacy Network** |
| **Contact Name** | **Anthony Campbell, PharmD, BCSCP** |
| **Contact Phone** | **352-622-2913** |
| **Contact Email** | **ACampbell@wellsrx.com** |

| 503A Bulk Drug Substance Nomination | |
|---|---|
| What is the name of the nominated ingredient? | **L-Theanine** |
| Is the ingredient an active ingredient that meets the definition of "bulk drug substance" in 207.3 (a)(4)? | **YES** |
| Is the ingredient listed in any of the three sections of the Orange Book? | **No** |
| Were any drug monographs for the ingredient found in the USP or NF monographs? | **No** |
| What is the chemical name of the substance? | **IUPAC Name:**<br>(2*S*)-2-amino-5-(ethylamino)-5-oxopentanoic acid<br><br>**InChIKey**<br>DATAGRPVKZEWHA-YFKPBYRVSA-N<br><br>**CAS#: 3081-61-6**<br><br>$C_7H_{14}N_2O_3$ |
| What is the common name of the substance? | L-Theanine<br>3081-61-6<br>Theanine<br>Theanin<br>Suntheanine<br>N-Ethyl-L-glutamine |
| Does the substance have a UNII code? | 8021PR16QO |
| What is the chemical grade of the substance? | **Provided by FDA Registered Supplier/COA** |
| What is the strength, quality, stability, and purity of the ingredient? | **Assay, Description, Solubility, etc.; Example of Certificate of Analysis for this chemical is attached.** |
| How is the ingredient supplied? | **Raw chemical/powder** |
| Is the substance recognized in foreign pharmacopeias or registered in other countries? | **European Chemicals Agency (ECHA)**<br>221-379-0<br>**Source: European Chemicals Agency (ECHA)**<br>**Record Name: N-ethyl-L-glutamine**<br>**URL: https://echa.europa.eu/substance-information/-/substanceinfo/100.019.436** |

| | |
|---|---|
| | Description: *The European Chemicals Agency (ECHA) is an agency of the European Union which is the driving force among regulatory authorities in implementing the EU's groundbreaking chemicals legislation for the benefit of human health and the environment as well as for innovation and competitiveness.* |
| Has information been submitted about the substance to the USP for consideration of drug monograph development? | No/Unknown |
| What dosage form(s) will be compounded using the bulk drug substance? | Tablet<br>Cream<br>Injection<br>Solution<br>Capsule |
| What strength(s) will be compounded from the nominated substance? | Tablet: 2.5mg sublingual tablet<br>Cream: 10%<br>Injection: 75mg vial (10mg/mL)<br>Capsule: 50mg, 100mg, & 200mg |
| What is the anticipated route(s) of administration of the compounded drug product(s)? | Sublingual<br>Topical<br>Subcutaneous/Intramuscular<br>Oral |
| Are there safety and efficacy data on compounded drugs using the nominated substance? | The Food and Drug Administration (FDA) considers L-THEANINE to be generally recognized as safe (GRAS) and allows its sale as a dietary supplement.<br><br>**Generally recognized as safe** (**GRAS**) is a United States Food and Drug Administration (FDA) designation that a chemical or substance added to food is considered safe by experts under the conditions of its intended use. An ingredient with a GRAS designation is exempted from the usual Federal Food, Drug, and Cosmetic Act (FFDCA) food additive tolerance requirements.<br><br>Theanine, a precursor of ethylamine, is found in green tea. It has gone under investigation in clinical trial NCT00291070 (Effects of L-Theanine in Boys With ADHD). |
| Has the bulk drug substance been used previously to compound drug product(s)? | YES |
| What is the proposed use for the drug product(s) to be compounded with the nominated substance? | Relaxation/Anxiety/Sleep/Calming |
| What is the reason for use of a compounded drug product rather than an FDA-approved product? | no FDA-approved product available |
| Is there any other relevant information? | Widely available and safely used as a dietary supplement |

MEDISCA®

# CERTIFICATE OF ANALYSIS

## THEANINE (L) (98%)

| | |
|---|---|
| Batch/Lot Number : | 188495 |
| Manufacturing Date : | 11/02/2020 |
| Expiration Date : | 10/31/2023 |
| CAS: | 3081-61-6 |

| TESTS | SPECIFICATIONS | RESULTS |
|---|---|---|
| ASSAY ON DRIED BASIS | 98.00 - 102.00 % | 99.63 % |
| DESCRIPTION | White to off-white, odourless, crystalline powder. | CONFORMS |
| IDENTIFICATION <197A>** | IR: Reference to standard spectrum. | POSITIVE |
| BULK DENSITY | To be reported. | 0.24 g/ml |
| TAPPED DENSITY | To be reported. | 0.48 g/ml |
| SPECIFIC ROTATION | +7.5° to +8.5° | + 7.96° |
| MELTING POINT | 200° - 210 °C | 202.4° - 202.6 °C |
| pH | 5.0 - 6.0 | 5.7 |
| CHLORIDE | <= 0.02 % | < 0.02 % |
| IRON | <= 0.001 % | < 0.001 % |
| LOSS ON DRYING | <= 1.00 % | 0.24 % |
| RESIDUE ON IGNITION | <= 0.20 % | 0.07 % |
| ELEMENTAL IMPURITIES <232>* | Meets the requirements | CONFORMS |
| TOTAL PLATE COUNT | <= 1000 cfu/g | < 1000 cfu/g |
| YEAST AND MOLD | <= 100 cfu/g | < 100 cfu/g |

## LOT TESTED BY:

CED Analytical Laboratory Inc.
6641 N Beltline Rd Unit 130
Irving, TX 75063

## PUBLISHED BY:

## PUBLISHED DATE:

05/06/2022

## ISSUE DATE:

11/12/2021

The above mentioned product conforms to the manufacturer's specifications.

The above test results are a direct transcription of information provided to MEDISCA from the Certificate of Analysis provided by the manufacturer / supplier. Additional testing conducted by MEDISCA is represented by an asterisk.

All dates in this document are in format mm/dd/yyyy unless otherwise specified

This document has been electronically approved through MEDISCA's Quality Management System.

MEDISCA®

# CERTIFICATE OF ANALYSIS

## THEANINE (L) (98%)

| | |
|---|---|
| Batch/Lot Number : | 188495 |
| Manufacturing Date : | 11/02/2020 |
| Expiration Date : | 10/31/2023 |
| CAS: | 3081-61-6 |

| TESTS | SPECIFICATIONS | RESULTS |
|---|---|---|
| ABSENCE OF SPECIFIED MICROORGANISMS | Meets the requirements for the absence of:<br>• Staphylococcus aureus<br>• E.coli<br>• Salmonella<br>• Coliforms | CONFORMS |
| PARTICLE SIZE | 90 % through 60 mesh. | CONFORMS |
| RESIDUAL SOLVENTS | Meets the requirements | CONFORMS |
| SOLUBILITY | Very easily soluble in water. | |
| **PACKAGING AND STORAGE** | Preserve in tight, light-resistant containers. | |
| *TESTED ON 11/11/2021 | | |
| **TESTED ON 05/05/2022 | | |
| Lot number has been changed from 010095-H2020110901 to 188495. | | |

## LOT TESTED BY:

CED Analytical Laboratory Inc.
6641 N Beltline Rd Unit 130
Irving, TX 75063

## PUBLISHED BY:

## PUBLISHED DATE:

05/06/2022

## ISSUE DATE:

11/12/2021

The above mentioned product conforms to the manufacturer's specifications.

The above test results are a direct transcription of information provided to MEDISCA from the Certificate of Analysis provided by the manufacturer / supplier. Additional testing conducted by MEDISCA is represented by an asterisk.

All dates in this document are in format mm/dd/yyyy unless otherwise specified

This document has been electronically approved through MEDISCA's Quality Management System.