

RESEARCH MONOGRAPH . COMPOUND PROFILE

Cogitum

A potassium salt of N-acetyl-DL-aminosuccinic acid developed in France as an oral neurometabolic tonic for asthenic syndrome, cognitive fatigue, and pediatric neurodevelopmental delay, distinguished by its structural relationship to endogenous N-acetylaspertate and downstream modulation of glutamatergic and myelinogenic pathways.

DOCUMENT	KDC-MN-1582
ISSUED	2026-05-20
REVISION	1.0
AUTHOR	Kodiac biolabs Research
COMPOUND CLASS	Acetylated amino acid derivative; synthetic N-acetylaspertate analog with neurometabolic and adaptogenic activity

ABSTRACT

Cogitum is the proprietary pharmaceutical preparation of potassium N-acetyl-DL-aminosuccinate (bipotassium acetylaminosuccinate), a synthetic analog of N-acetylaspartate (NAA), the most concentrated free amino acid derivative in the mammalian central nervous system. The compound was developed in France and patented in the United States in 1969 (US 3,433,875) for the improvement of mental performance in adults experiencing intellectual overwork, memory disorders, and cognitive decline associated with senescence. The active substance provides an exogenous source of the acetylated aspartate moiety that participates in neuronal energy metabolism through the tricarboxylic acid cycle, serves as the obligate precursor for myelin lipid synthesis via oligodendrocytic aspartoacylase-mediated deacetylation, functions as an osmolyte maintaining neuronal volume homeostasis, and is the direct biosynthetic precursor of N-acetylaspartylglutamate (NAAG), the most abundant neuropeptide in the human brain and an endogenous agonist at the presynaptic metabotropic glutamate receptor type 3 (mGluR3). Cogitum is classified pharmacologically as a tonic agent and adaptogen; it is registered and marketed as a drinkable oral solution (250 mg per 10 mL ampoule) in France, Portugal, and several other jurisdictions, and is used extensively in Russian neuropsychiatric practice for the treatment of asthenic syndrome, attention deficit hyperactivity disorder with subclinical epileptiform activity, speech and language delay, and neurodevelopmental disorders in children aged seven years and older.

The clinical evidence base includes a 2023 double-blind, randomized, placebo-controlled trial demonstrating that potassium N-acetylaminosuccinate at 750 mg daily for 21 days significantly reduced fatigue scores and improved complex cognitive functions in adults with asthenic syndrome compared to placebo, with no reported adverse events (Esin et al., 2023). Pediatric evidence comprises a 249-patient study in children with ADHD and subclinical epileptiform electroencephalographic activity demonstrating significant improvements in attention, memory, and speech without aggravation of epileptiform discharges or provocation of seizures; additional cohort studies in children with speech delay, traumatic brain injury sequelae, mental retardation, and schizotypal spectrum disorders have reported efficacy in improving cognitive and linguistic performance. The pharmacological rationale rests on the established neurobiology of endogenous N-acetylaspartate: NAA concentrations in the brain reach 10 millimolar or greater, are confined almost exclusively to neurons, and serve as the principal magnetic resonance spectroscopy marker of neuronal viability; reduced NAA is a consistent finding in neurodegenerative disease, traumatic brain injury, multiple sclerosis, and neurodevelopmental disorders. The exogenous provision of the acetylaminosuccinate moiety is hypothesized to support neuronal mitochondrial energy production, to provide acetate substrate for oligodendrocytic myelin lipid synthesis, and to augment NAAG-mediated glutamatergic neuromodulation.

Safety data across pediatric and adult populations demonstrate excellent tolerability. The compound has no reported cases of overdose toxicity, produces no clinically significant drug interactions at registered doses, and is contraindicated only in cases of known hypersensitivity to the active substance or

excipients. The principal limitation of the evidence base is the concentration of clinical research in Russian-language journals with limited replication in Western multicenter trial frameworks. This monograph documents the chemistry, synthesis, mechanism, pharmacokinetics, clinical evidence, sourcing, reconstitution, stack interactions, adverse events, and comparative assessment of Cogitum against five neurometabolic and nootropic alternatives on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Proprietary name: Cogitum.

International Nonproprietary Name equivalent: Potassium acetylaminosuccinate (not formally assigned an INN by the World Health Organization; the compound predates modern INN nomenclature for this class).

Chemical name (IUPAC): Dipotassium 2-(acetylamino)succinate; alternatively, bipotassium N-acetyl-DL-aminosuccinate.

Synonyms: Acetylamino succinic acid dipotassium salt; potassium N-acetylaminosuccinate; bipotassium acetylaminosuccinate; N-acetyl-DL-aspartic acid dipotassium salt.

Development and patent identifiers: US Patent 3,433,875 (filed 1966, granted 1969), assigned to the original French developer. The patent describes the administration of potassium N-acetyl-DL-aminosuccinate for the improvement of mental performance in adults experiencing intellectual overwork, memory and ideation disorders, and cognitive decline associated with senescence [1].

Chemical Abstracts Service registry number: The dipotassium salt of N-acetyl-DL-aminosuccinic acid does not carry a widely cited CAS number in major English-language chemical databases; the free acid N-acetyl-DL-aspartic acid is registered under CAS 997-55-7 (DL-form) and the L-enantiomer N-acetyl-L-aspartic acid under CAS 997-55-7. The dipotassium salt is catalogued as bipotassium N-acetylaminosuccinate in specialty chemical reference sources with molecular formula $C_6H_7K_2NO_5$ [2].

Pharmacological classification: Tonic agents and adaptogens (Russian pharmacological classification); general CNS stimulants and neurometabolic agents (French classification).

1.2 Structural class and chemistry

Cogitum's active substance is the dipotassium salt of N-acetyl-DL-aminosuccinic acid. The compound belongs to the structural class of acetylated amino acid derivatives, specifically the N-acetylated dicarboxylic amino acids. It is a synthetic racemic analog of endogenous N-acetyl-L-aspartic acid (NAA), the most concentrated free amino acid derivative in the mammalian central nervous system.

Molecular formula: C₆H₇K₂NO₅ (dipotassium salt); C₆H₉NO₅ (free acid).

Molecular weight: 251.32 g/mol (dipotassium salt); 175.14 g/mol (free acid).

Physical properties: White to off-white crystalline powder. Freely soluble in water; the dipotassium salt is formulated as a clear, colorless to pale yellow aqueous oral solution at 25 mg/mL (250 mg per 10 mL ampoule). The solution has a banana flavor imparted by added flavorant and contains fructose (1 g per ampoule) and methyl parahydroxybenzoate (15 mg per ampoule) as preservative.

Stereochemistry: The pharmaceutical preparation contains the DL-racemic mixture of N-acetylaminosuccinic acid. The endogenous brain metabolite is exclusively the L-enantiomer (N-acetyl-L-aspartic acid). The racemic formulation provides both enantiomers; the L-form is the biologically active isomer that corresponds to the endogenous neurometabolite, while the D-form is pharmacologically inert and is presumably eliminated without significant biological activity. The use of the racemic mixture in the pharmaceutical preparation reflects the original synthetic approach and the absence of enantioselective synthetic optimization in the development era.

1.3 Synthesis

The synthesis of potassium N-acetyl-DL-aminosuccinate proceeds through acetylation of DL-aspartic acid (DL-aminosuccinic acid) with acetic anhydride or acetyl chloride under basic conditions, followed by neutralization with potassium hydroxide or potassium carbonate to form the dipotassium salt [1]. The synthetic route is straightforward:

Stage 1: DL-aspartic acid is dissolved or suspended in aqueous or aqueous-organic solvent (water, acetic acid, or pyridine as co-solvent). Acetic anhydride is added at controlled temperature (0 to 25 degrees Celsius) with stirring. The N-acety-

lation proceeds at the alpha-amino group to yield N-acetyl-DL-aspartic acid (N-acetylaminosuccinic acid) in high yield (typically greater than 90 percent).

Stage 2: The free diacid is neutralized with two equivalents of potassium hydroxide (or potassium bicarbonate) to form the water-soluble dipotassium salt. The product is recovered by crystallization from water-ethanol mixtures or by lyophilization.

Stage 3: The dipotassium salt is dissolved in purified water at 25 mg/mL, combined with fructose (100 mg/mL), methyl parahydroxybenzoate (1.5 mg/mL), and banana flavor (0.7 mg/mL), and filled into sealed glass ampoules (10 mL per ampoule). The ampoules are sealed by flame or mechanical crimp and sterilized by terminal autoclaving or sterile filtration.

The industrial synthesis is well established and the raw materials (DL-aspartic acid, acetic anhydride, potassium hydroxide) are inexpensive commodity chemicals. The compound does not present significant manufacturing complexity.

2. Abstract

Cogitum (potassium N-acetyl-DL-aminosuccinate) is a synthetic analog of N-acetylaspartate (NAA), the most abundant free amino acid derivative in the mammalian brain, formulated as an oral solution for the treatment of asthenic syndrome, cognitive fatigue, and neurodevelopmental disorders. The compound was developed in France in the 1960s, patented for the improvement of mental performance (US 3,433,875; 1969), and has been marketed as a drinkable ampoule preparation (250 mg/10 mL) in France, Portugal, and the Russian Federation for over five decades [1].

The pharmacological rationale is grounded in the established neurobiology of endogenous N-acetylaspartate: NAA is synthesized exclusively in neuronal mitochondria from L-aspartate and acetyl-coenzyme A by the enzyme L-aspartate N-acetyltransferase (Nat8L); it is present at concentrations of 5 to 15 millimolar in the healthy brain; it is catabolized exclusively in oligodendrocytes by aspartoacylase (ASPA) to yield free acetate (used for myelin lipid synthesis) and L-aspartate; and it serves as the obligate precursor for enzymatic synthesis of N-acetylaspartylglutamate (NAAG), the most concentrated neuropeptide in the human brain and an endogenous selective agonist at the presynaptic metabotropic glutamate receptor type 3 (mGluR3) [3, 4, 5]. Deficiency or reduction of brain NAA concentrations is a consistent finding in neurodegenerative diseases (Alzheimer's disease, multiple sclerosis, Huntington's disease), traumatic brain injury, schizophrenia, and pediatric neurodevelopmental disorders; NAA measured by proton magnetic resonance spectroscopy is the principal non-invasive biomarker of neuronal viability and density in clinical neuroimaging [6].

The clinical evidence base includes a 2023 double-blind placebo-controlled trial demonstrating efficacy of 750 mg daily for 21 days in adult asthenic syndrome [7]; a 249-patient pediatric study demonstrating safety and efficacy in ADHD with sub-clinical epileptiform activity [8]; multiple cohort studies in pediatric speech delay, traumatic brain injury sequelae, and neurodevelopmental disorders [9, 10, 11]; and a 2025 analysis of efficacy across mental disorders in childhood including autistic spectrum and schizotypal spectrum conditions [12]. The compound is well tolerated across age groups, with allergic skin reactions as the sole reported adverse event at very low frequency; no cases of overdose toxicity have been documented. The compound is not approved by the United States Food and Drug Administration

and has not undergone formal evaluation by the European Medicines Agency under centralized procedure; it is registered as a medicine at national level in France, Portugal, and the Russian Federation.

3. Discovery and Development History

3.1 Origin and patent

The active substance of Cogitum, potassium N-acetyl-DL-aminosuccinate, was developed in France in the mid-1960s. The original US patent (US 3,433,875), filed in 1966 and granted on March 18, 1969, describes the compound as an agent for the improvement of mental performance and specifies its administration to adults experiencing intellectual overwork, memory and ideation capacity disorders, and cognitive decline of senescence [1]. The patent identifies the compound as having tonic and psychostimulant properties at oral doses of 500 to 1500 mg daily, delivered as a drinkable aqueous ampoule formulation.

3.2 Pharmaceutical development and registration

Cogitum was developed as a pharmaceutical specialty by the French manufacturer (historically associated with Sanofi predecessors) and registered in France as an oral solution for the treatment of functional asthenic states. The registration occurred prior to the establishment of the European Medicines Agency centralized procedure and was maintained at national level under French drug regulatory authority (now ANSM). The product was subsequently registered in Portugal under the same proprietary name and in several other francophone and lusophone jurisdictions.

3.3 Adoption in Russian neuropsychiatry

Beginning in the 2000s, Cogitum achieved extensive clinical adoption in the Russian Federation for pediatric neurology applications. The Russian regulatory framework registered the compound as a tonic and adaptogen, and clinical practice expanded the indications to include attention deficit hyperactivity disorder, speech and language delay, traumatic brain injury sequelae in children, autism spectrum conditions, and schizotypal spectrum disorders [9, 10, 11, 12]. The Russian clinical literature on Cogitum is substantially larger than the Western European literature and represents the majority of published clinical evidence. The compound is pre-

scribed in Russian neuropsychiatric practice at doses of 250 mg (one ampoule) daily for children aged 7 to 10 years and 500 mg (two ampoules) daily for children and adolescents aged 10 to 18 years, with treatment courses of 14 to 30 days [10].

3.4 Scientific context: N-acetylaspartate research

The pharmacological rationale for Cogitum gained substantial scientific support from the parallel development of NAA neurobiology research. The identification of NAA as the principal magnetic resonance spectroscopy marker of neuronal viability (Tallan et al., 1956; later validated by extensive clinical MRS literature), the characterization of its role in myelin lipid synthesis through oligodendrocytic aspartoacylase catabolism (Matalon et al., 1988), the identification of Canavan disease as a deficiency of aspartoacylase leading to toxic NAA accumulation and spongy white matter degeneration [13, 14], and the characterization of NAAG as a neuromodulatory peptide acting at mGluR3 [5] collectively established the biological framework within which Cogitum's mechanism of action is understood.

4. Mechanism of Action

Cogitum provides an exogenous source of the N-acetylaspartate moiety. The proposed mechanisms of action are multiple and reflect the established biological roles of endogenous NAA in the central nervous system.

4.1 Neuronal energy metabolism

N-acetylaspartate is synthesized in neuronal mitochondria from L-aspartate and acetyl-coenzyme A by L-aspartate N-acetyltransferase (Nat8L, also designated aspartate N-acetyltransferase). The acetylation of aspartate facilitates its removal from the mitochondrial matrix, thereby relieving product inhibition of the aspartate aminotransferase reaction and favoring the conversion of oxaloacetate to aspartate with concomitant regeneration of alpha-ketoglutarate from glutamate [3, 6]. This metabolic coupling links NAA synthesis to the tricarboxylic acid (TCA) cycle and to neuronal ATP production. Exogenous provision of acetylaminosuccinate may support this metabolic node under conditions of neuronal energy stress, contributing to the anti-asthenic and cognitive-enhancing effects observed clinically.

4.2 Myelin lipid synthesis

Following synthesis in neurons, NAA is transported to the extracellular space and taken up by oligodendrocytes, where it is hydrolyzed by aspartoacylase (ASPA, EC 3.5.1.15) to yield free L-aspartate and acetate. The liberated acetate is converted to acetyl-CoA by acetyl-CoA synthetase and used as the carbon source for fatty acid synthesis (principally very-long-chain fatty acids and their derivatives) required for myelin membrane assembly and maintenance [14, 15]. This metabolic pathway is the principal source of acetyl groups for myelin lipid synthesis during postnatal myelination and continues to supply acetate for myelin lipid turnover in the adult brain. Exogenous acetylaminosuccinate may augment this supply, supporting myelinogenic processes in developing and remyelinating nervous systems. This mechanism is particularly relevant to the pediatric indications (speech delay, neurodevelopmental disorders) where white matter maturation is ongoing.

4.3 NAAG synthesis and glutamatergic neuromodulation

NAA is the obligate precursor for the enzymatic synthesis of N-acetylaspartylglutamate (NAAG), catalyzed by NAAG synthetase (RIMKLA and RIMKLB enzymes). NAAG is the most abundant neuropeptide in the mammalian brain, present at millimolar concentrations in cortex, hippocampus, and spinal cord [5]. Upon release from glutamatergic synaptic terminals, NAAG acts as a selective agonist at the presynaptic metabotropic glutamate receptor type 3 (mGluR3, also designated GRM3), providing negative feedback inhibition of glutamate release. This neuromodulatory function is neuroprotective under conditions of excessive glutamatergic transmission and is hypothesized to contribute to the cognitive-stabilizing effects of the compound. Augmentation of the NAAG pool through exogenous NAA precursor provision may enhance this protective neuromodulatory tone [5, 16].

4.4 Osmoregulation

NAA functions as a significant neuronal osmolyte, contributing to the regulation of intracellular water volume in neurons. The high intracellular concentration (5 to 15 millimolar) and its charged state at physiological pH make NAA an effective participant in cell volume regulation [6]. This osmoregulatory function is relevant to the maintenance of neuronal membrane integrity under conditions of metabolic stress or edema.

4.5 Composite mechanism

The composite mechanism of Cogitum is therefore a multi-pathway neurometabolic support function: provision of substrate for neuronal energy metabolism (TCA cycle coupling), supply of acetate for myelin lipid synthesis, augmentation of NAAG-mediated glutamatergic neuromodulation, and osmolytic volume support. These multiple downstream consequences from a single molecular precursor distinguish the compound from receptor-targeted pharmacological agents and position it as a metabolic substrate therapy rather than a classical receptor agonist or antagonist. The clinical consequences (anti-asthenic effect, cognitive improvement, support for neurodevelopmental maturation) are consistent with this multi-pathway metabolic mechanism.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Cogitum is administered orally as a drinkable aqueous solution. The active substance (potassium N-acetylaminosuccinate) is a small, highly water-soluble dipotassium amino acid salt with molecular weight 251.32 g/mol, properties that predict rapid and complete absorption from the gastrointestinal tract. Formal bioavailability studies specific to the Cogitum formulation are not available in the indexed English-language literature. By analogy with the pharmacokinetics of orally administered aspartic acid (bioavailability approximately 24 percent as the free amino acid in rat models) and with small acetylated amino acid derivatives, absorption is expected to be rapid with time to peak plasma concentration of 1 to 2 hours [17].

5.2 Distribution

No specific volume of distribution data are published for potassium N-acetylaminosuccinate in humans. Endogenous NAA is present in the brain at concentrations of 5 to 15 millimolar and is synthesized exclusively within neurons; the blood-brain barrier transport of exogenous N-acetylaspargate has been studied in rodent models and appears to involve both passive diffusion and carrier-mediated transport (putative dicarboxylic acid transporters). Central nervous system penetration of the exogenously administered compound is necessary for the proposed mechanism but has not been formally demonstrated in human pharmacokinetic studies with labeled compound. The clinical efficacy observed in multiple trials is indirect evidence of central nervous system bioavailability at therapeutically relevant concentrations [7, 8].

5.3 Metabolism

Exogenous N-acetylaminosuccinate is expected to undergo the same metabolic fate as endogenous NAA: hydrolysis by aspartoacylase (ASPA) in oligodendrocytes and other tissues to yield free L-aspartate and acetate. The L-aspartate enters general amino acid metabolism (transamination, gluconeogenesis, urea cycle); the acetate is activated to acetyl-CoA for lipid synthesis or enters the TCA cycle. Additional hydrolysis by non-specific acylases in liver and kidney is also expected. The D-enantiomer present in the racemic formulation is metabolized by D-aspartate oxidase or excreted unchanged; it does not participate in the NAA-specific metabolic pathways.

5.4 Elimination

Elimination pathways include renal excretion of intact compound and of the metabolic products (L-aspartate conjugates, acetate, carbon dioxide). No specific urinary recovery or elimination half-life data are published for the pharmaceutical preparation. The compound is not expected to accumulate significantly given its small molecular weight, high water solubility, and the ubiquity of the metabolic enzymes.

5.5 Route of administration

Cogitum is formulated exclusively for oral administration as a drinkable solution in sealed glass ampoules (10 mL per ampoule, containing 250 mg active substance). The ampoule tips are scored for breakage; the solution is consumed directly from the ampoule or diluted in water. No parenteral, intramuscular, subcutaneous, or intravenous formulation is marketed. The compound's mechanism (metabolic substrate provision) does not require precise plasma concentration targeting, making the oral route appropriate for the intended pharmacological effect.

5.6 Dosing

Adults: 750 mg daily (three ampoules), taken in the morning, for 21 days as a standard treatment course. Extension to 28 to 30 days is practiced in clinical settings. Some protocols use 500 mg daily (two ampoules) for milder asthenic states [7].

Children aged 7 to 10 years: 250 mg daily (one ampoule), taken in the morning [10].

Children and adolescents aged 10 to 18 years: 500 mg daily (two ampoules), taken in the morning [10].

Treatment courses are typically 14 to 30 days in duration; repeated courses may be administered after intervals of 1 to 3 months as clinically indicated.

6. Preclinical Pharmacology

6.1 In vivo models

Preclinical evidence for Cogitum derives primarily from the broader NAA and NAAG research literature rather than from dedicated preclinical studies of the pharmaceutical preparation. The following findings from NAA research are relevant to the mechanism and support clinical application:

Animal models of Canavan disease (aspartoacylase knockout mice) demonstrate that NAA accumulation produces spongy white matter degeneration, confirming the tight coupling between NAA catabolism and myelin homeostasis [13, 14]. Conversely, conditions of reduced NAA (traumatic brain injury models, excitotoxic lesion models) are associated with neuronal loss and cognitive impairment, and interventions that restore NAA levels correlate with functional recovery [6].

NAAG administration in rodent models produces neuroprotection against excitotoxicity through mGluR3-mediated reduction of glutamate release [5, 16]. Inhibitors of NAAG peptidase (the enzyme that degrades NAAG to NAA and glutamate) similarly produce neuroprotection and cognitive enhancement in multiple rodent paradigms, supporting the therapeutic relevance of augmenting NAAG signaling.

6.2 In vitro studies

In vitro studies of NAA demonstrate its role as a protein aggregation inhibitor (potentially relevant to neurodegenerative disease) and as a metabolic coupling factor between neurons and oligodendrocytes in co-culture systems. NAA release from neurons and uptake by oligodendrocytes has been demonstrated in mixed cortical cultures, confirming the intercellular metabolic shuttle mechanism [15].

6.3 Relevance to Cogitum

The preclinical evidence base is indirect: it establishes the biological importance of the NAA metabolic system and provides mechanistic support for the hypothesis that exogenous NAA substrate provision can support neuronal and oligodendrocytic function. Direct preclinical efficacy studies of potassium N-acetylaminosuc-

nate (the Cogitum active substance) in animal cognitive or behavioral models are not extensively published in indexed journals. The clinical evidence (Section 7) provides the principal efficacy support.

7. Clinical Evidence Base

7.1 Asthenic syndrome in adults

The principal registration-quality clinical evidence is the Esin et al. (2023) double-blind, randomized, placebo-controlled trial of potassium N-acetylaminosuccinate (Cogitum) in adults with asthenic syndrome [7]. Patients received either Cogitum at 750 mg daily or placebo for 21 days. The Cogitum group demonstrated statistically significant reduction in fatigue severity scores and improvement in complex cognitive functions (assessed by neuropsychological testing battery) compared to the placebo group, in which no statistically significant changes were observed. A placebo effect was noted in 10 patients (29.4 percent) of the control group, which is consistent with the expected placebo response rate in fatigue and cognitive function trials. The compound was well tolerated with no reported adverse events in the treatment group. This trial provides Level 1b evidence (single adequate RCT) for efficacy in adult asthenic syndrome.

7.2 ADHD with subclinical epileptiform activity

A study of 249 children with attention deficit hyperactivity disorder (ADHD) and subclinical epileptiform activity on electroencephalography evaluated the efficacy and safety of Cogitum [8]. The compound demonstrated significant improvement in attention, memory, and speech measures. Critically, none of the 249 children experienced aggravation of epileptiform activity or developed epileptic seizures during treatment. This finding establishes Cogitum as a safe medication for cognitive and attentional enhancement in the specific clinical context of ADHD comorbid with subclinical epileptiform discharges, a population in which many stimulant and nootropic agents carry seizure risk concerns.

7.3 Speech and language delay in children

Bobylova et al. (Russian Journal of Child Neurology) evaluated Cogitum in children with speech disorders of various etiologies [9]. The treatment course produced improvements in expressive and receptive language measures, consistent with the compound's proposed mechanism of supporting white matter maturation and neu-

ral network connectivity through the myelin lipid synthesis pathway. The study was open-label and cohort-based; it provides Level 3 evidence (non-randomized controlled or observational study) for efficacy in pediatric speech delay.

7.4 Pediatric neurology and psychiatry

Goryunova and Shevchenko (2019) published a comprehensive report of clinical experience with Cogitum in children's neurology and psychiatry [10]. The study included children with traumatic brain injury sequelae, mental retardation, ADHD, and schizotypal spectrum disorders. Cogitum demonstrated efficacy across these diverse indications in improving cognitive performance, attention, and adaptive function, with a favorable safety profile. The 2025 publication by Zavadenko and colleagues in the Korsakov Journal of Neurology and Psychiatry extended this evidence to a systematic analysis of Cogitum across mental disorders in childhood, including autistic spectrum conditions [12].

7.5 Intellectual overwork and cognitive fatigue

The original patent indication (improvement of mental performance in adults experiencing intellectual overwork) has been supported by clinical use data over five decades of marketing in France and Portugal [1]. Formal controlled trial data for this specific indication beyond the Esin 2023 asthenic syndrome trial are limited in the indexed English-language literature, though clinical practice experience and pharmacovigilance data support efficacy and safety in this population.

7.6 Post-COVID chronic fatigue

A 2023 prospective randomized double-blind placebo-controlled study evaluated neuroprotective therapy (including compounds in the Cogitum class) for chronic fatigue syndrome following COVID-19 infection, using functional brain MRI as an outcome measure [18]. This emerging indication is consistent with the compound's anti-asthenic mechanism and may represent a new clinical application in the context of post-infectious cognitive and fatigue syndromes.

7.7 Limitations of the evidence base

The clinical evidence for Cogitum is concentrated in Russian-language journals with limited representation in high-impact Western medical journals. The single double-blind placebo-controlled trial (Esin 2023) provides Level 1b evidence for adult asthenic syndrome; other evidence is Level 3 or Level 4 (cohort studies, case series, clinical experience reports). Large multicenter randomized controlled trials with internationally standardized cognitive and neurodevelopmental outcome measures have not been conducted. The compound has not been evaluated by the European Medicines Agency centralized procedure or by the United States Food and Drug Administration, and the regulatory pathway reflects the historical French national registration rather than modern evidence-based medicine standards. Investigators considering Cogitum for research should weight the evidence accordingly.

8. Sourcing and Quality Verification

8.1 Pharmaceutical-grade sourcing

Cogitum is available as the branded pharmaceutical product (Cogitum, oral solution, 250 mg/10 mL ampoules, boxes of 30 ampoules) from pharmacies in France, Portugal, and the Russian Federation. The pharmaceutical-grade product is the highest quality source and is appropriate for clinical research applications requiring regulatory equivalence to the marketed preparation. The product is manufactured to Good Manufacturing Practice (GMP) standards and carries a marketing authorization in its registered jurisdictions.

8.2 Research-grade sourcing

The active substance (bipotassium N-acetylaminosuccinate or N-acetyl-DL-aspartic acid dipotassium salt) is available from specialty chemical suppliers. N-acetyl-DL-aspartic acid (the free acid form) is catalogued by Sigma-Aldrich, Tokyo Chemical Industry (TCI), and other chemical suppliers at research-grade purity (greater than 98 percent by HPLC). The dipotassium salt may require custom synthesis by neutralization of the free acid with potassium hydroxide.

8.3 Quality verification

Investigators should confirm compound identity and purity through:

- High-performance liquid chromatography with ultraviolet detection, confirming area-percent purity greater than 98 percent
- Mass spectrometry confirmation of molecular weight (176.13 for the protonated free acid $[M+H]^+$; 251.32 for the dipotassium salt molecular formula weight)
- Nuclear magnetic resonance spectroscopy (1H and ^{13}C) confirming the expected resonances for the N-acetylaspargate structure
- Karl Fischer analysis for residual water content
- Potassium content determination by atomic absorption spectroscopy or ion chromatography (expected: 31.1 percent by weight for the dipotassium salt)

- Chiral HPLC or polarimetry if enantiopure (L-form only) material is required for mechanistic studies

8.4 Storage

The pharmaceutical product is stored at room temperature (15 to 25 degrees Celsius) protected from light, in the original sealed glass ampoules. Shelf life of the marketed product is 3 years from date of manufacture. The bulk active substance (solid powder) should be stored at 2 to 8 degrees Celsius in a desiccated container; stability at room temperature is acceptable for short-term use.

9. Reconstitution and Handling

9.1 Pharmaceutical formulation

Cogitum is supplied as a ready-to-use oral solution that does not require reconstitution. Each 10 mL sealed glass ampoule contains:

- Potassium acetylaminosuccinate: 250 mg (active substance)
- Fructose: 1000 mg (excipient, sweetener)
- Methyl parahydroxybenzoate: 15 mg (preservative)
- Banana flavor: 7 mg (flavorant)
- Purified water: to 10 mL (vehicle)

The ampoule tips are scored and broken open for oral administration. The solution is consumed directly or mixed with a small volume of water (half a glass).

9.2 Research-grade preparation

For research applications requiring custom formulations:

Aqueous stock solution: Dissolve the dipotassium salt in purified water or phosphate-buffered saline at concentrations up to 100 mg/mL (the high aqueous solubility of the dipotassium salt permits concentrated stock preparation). Filter-sterilize through 0.22-micrometer membrane for sterile applications. Store at 2 to 8 degrees Celsius; use within 14 days of preparation.

Cell culture applications: Prepare stock solutions in sterile water or cell culture-grade saline; adjust pH to 7.0 to 7.4 if required (the dipotassium salt is near-neutral in aqueous solution). Dilute to working concentrations (typically 1 to 10 millimolar for in vitro NAA-related research) in cell culture medium immediately before use.

Stability: Aqueous solutions of potassium N-acetylaminosuccinate are chemically stable at neutral pH and refrigerated temperature for at least 30 days. The amide bond linking the acetyl group to the amino acid is resistant to non-enzymatic hydrolysis at physiological pH. Avoid strongly acidic conditions (pH below 2) where acid-catalyzed hydrolysis may release free aspartic acid and acetic acid.

9.3 Handling precautions

The compound presents no significant handling hazards. It is not volatile, not corrosive, and not a known sensitizer by dermal or inhalation routes. Standard laboratory personal protective equipment (gloves, laboratory coat, eye protection) is appropriate. No special ventilation or containment requirements apply.

10. Stack Interactions and Combinations

10.1 Pharmacokinetic interactions

Cogitum's active substance is a small amino acid derivative metabolized by ubiquitous hydrolytic enzymes (aspartoacylase, non-specific acylases) rather than by cytochrome P450 enzymes. No significant CYP450-mediated drug interactions are expected or reported. The compound does not inhibit or induce CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 at therapeutically relevant concentrations.

10.2 Pharmacodynamic interactions

Glutamatergic agents: The NAAG-mGluR3 pathway provides negative modulation of glutamate release. Concurrent administration with glutamatergic NMDA receptor antagonists (memantine, ketamine) or with other agents that modulate glutamatergic tone (riluzole, lamotrigine) could theoretically produce additive effects on glutamate signaling. No clinical interaction data are available; the combination has not been formally studied.

Other nootropic and neurometabolic agents: Cogitum is frequently combined in Russian neuropediatric practice with other neurometabolic agents (pantogam, encephabol, cortexin, cerebrolysin). No adverse interactions have been reported in clinical use. The metabolic substrate mechanism of Cogitum is complementary to receptor-targeted nootropics (piracetam, aniracetam) and to peptide neurotrophic agents (cerebrolysin, cortexin); additive or synergistic effects on cognitive endpoints are plausible but not formally demonstrated in controlled trials.

Anticonvulsants: The 249-patient ADHD study with subclinical epileptiform activity [8] established that Cogitum does not aggravate epileptiform discharges and does not provoke seizures. Concurrent use with anticonvulsant medications (valproate, levetiracetam, carbamazepine) is considered safe based on clinical experience.

Psychostimulants: Concurrent use with methylphenidate or amphetamine derivatives for ADHD has not been formally studied. The metabolic mechanism of Cogitum is distinct from the catecholaminergic mechanism of psychostimulants; additive benefit on attention and cognition without pharmacokinetic interaction is plausible.

10.3 Dietary interactions

The fructose content of the pharmaceutical formulation (1 g per ampoule, 3 g daily at full adult dose) should be considered in patients with hereditary fructose intolerance. No other dietary interactions are reported.

10.4 Timing considerations

The compound is administered in the morning in clinical practice due to its mild psychostimulant and tonic properties; evening administration may produce insomnia in susceptible individuals. This timing preference reflects clinical experience rather than formal chronopharmacology data.

11. Adverse Events and Safety

11.1 Common adverse events

Cogitum demonstrates an exceptionally favorable safety profile across pediatric and adult populations:

- Allergic skin reactions (rash, urticaria, pruritus): reported at very low frequency (less than 1 percent of treated patients)
- Insomnia: rare, principally when administered in the evening rather than the morning
- No other common adverse events have been consistently reported across clinical studies

The Esin et al. (2023) double-blind placebo-controlled trial reported no adverse events in the treatment group [7]. The 249-patient pediatric ADHD study reported no aggravation of epileptiform activity and no seizures [8]. The cumulative clinical experience across five decades of marketing in France has not generated significant pharmacovigilance signals.

11.2 Serious adverse events

No serious adverse events have been reported in the published literature or in post-marketing pharmacovigilance data. No cases of overdose toxicity have been documented [10]. The development of toxic effects is not expected given the compound's nature as a simple acetylated amino acid derivative metabolized by ubiquitous hydrolytic enzymes to physiological metabolites (L-aspartate, acetate, potassium).

11.3 Contraindications

- Known hypersensitivity to potassium N-acetylaminosuccinate or to any excipient in the formulation (methyl parahydroxybenzoate, fructose, banana flavor)
- Children under 7 years of age (insufficient safety and efficacy data in younger children)
- Pregnancy (insufficient human data; not studied in pregnant women)

- Breastfeeding (compound excretion in human milk has not been characterized; breastfeeding should be discontinued during treatment)

11.4 Precautions

- Hereditary fructose intolerance: the formulation contains fructose (1 g per ampoule)
- Administration should be in the morning to minimize the risk of insomnia
- The methyl parahydroxybenzoate preservative may cause allergic reactions (possibly delayed) in sensitive individuals

11.5 Overdose

No cases of overdose have been reported. Given the metabolic substrate nature of the compound and the ubiquity of the catabolic enzymes, significant toxicity from acute overdose is not anticipated. Treatment would be supportive and symptomatic.

11.6 Long-term safety

Long-term safety data are derived from clinical practice experience in France (over 50 years) and in Russia (over 20 years). No chronic toxicity signals, organ damage, dependence, tolerance, or withdrawal phenomena have been reported. Treatment courses are typically 14 to 30 days in duration with rest periods; continuous long-term administration has not been formally evaluated in controlled studies.

12. Comparative Assessment

This section presents a structured comparative assessment of five neurometabolic and nootropic agents against Cogitum, evaluated on five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five comparators were selected as agents with overlapping indications (asthenic syndrome, cognitive enhancement, pediatric neurodevelopment) or overlapping mechanisms (neurometabolic substrate provision, neurotrophic support).

12.1 Piracetam (Nootropil)

Mechanism: Positive allosteric modulator of AMPA-type glutamate receptors; modulation of membrane fluidity and ion channel function; enhancement of mitochondrial electron transport chain efficiency. The mechanism is distinct from the metabolic substrate provision of Cogitum.

Development trajectory: Piracetam is the prototypical nootropic, developed by UCB Pharma in the 1960s and marketed globally for cognitive impairment, vertigo, cortical myoclonus, and learning disorders. It has been the subject of hundreds of clinical trials across diverse cognitive and neurological indications over six decades.

Novelty: Low. Piracetam is the oldest and most extensively studied nootropic compound. Its mechanism is well characterized but non-specific.

Effect size: Meta-analyses of piracetam in cognitive impairment and dementia have yielded inconsistent results; effect sizes are generally small (Cohen's d 0.1 to 0.3) and not consistently significant across populations. The Cochrane review of piracetam in dementia concluded insufficient evidence for routine clinical use.

Promising potential: Low to moderate. The compound remains marketed in many jurisdictions but is not considered first-line therapy for any cognitive indication in current evidence-based guidelines. Research interest has shifted to newer racetam derivatives and to mechanism-specific agents.

Side-effect profile: Generally well tolerated. Reported adverse events include psychomotor agitation, dysphoria, insomnia, gastrointestinal disturbance, and headache at higher doses. The profile is modestly less favorable than Cogitum's essentially absent adverse event signal.

Overall validation: Moderate. Extensive clinical and preclinical literature but inconsistent efficacy signals in rigorous trials.

Comparison to Cogitum: Piracetam has a receptor-modulatory mechanism (AMPA receptor PAM) distinct from Cogitum's metabolic substrate mechanism. Piracetam has substantially greater clinical trial volume but less consistent efficacy evidence. Cogitum has a more favorable safety profile and a more specific mechanistic rationale (NAA metabolic pathway support) but less total clinical evidence.

12.2 Cerebrolysin

Mechanism: Peptide neurotrophic preparation derived from porcine brain tissue; contains a standardized mixture of low-molecular-weight peptides and free amino acids with neurotrophic factor-like activity (BDNF-like, NGF-like, CNTF-like signaling).

Development trajectory: Developed by EVER Neuro Pharma (Austria); marketed in over 40 countries for stroke recovery, traumatic brain injury, dementia, and pediatric neurodevelopmental disorders. The clinical literature includes multiple randomized controlled trials in stroke (CASTA, CARS studies) and in traumatic brain injury.

Novelty: Moderate. The biological peptide preparation represents a multi-target neurotrophic approach distinct from single-mechanism agents. However, the undefined peptide composition limits mechanistic precision.

Effect size: Moderate. The CASTA trial in acute ischemic stroke demonstrated improvement on ARAT scores; meta-analyses suggest modest cognitive improvement in vascular and Alzheimer's dementia. Effect sizes are generally in the Cohen's d 0.2 to 0.4 range.

Promising potential: Moderate. Active clinical development continues; new trials in post-COVID neurological sequelae and in pediatric neurodevelopment are ongoing.

Side-effect profile: Generally well tolerated parenterally. Reported adverse events include vertigo, agitation, feeling of heat, and injection-site reactions. Requires intramuscular or intravenous administration (no oral formulation), which is a practical disadvantage relative to Cogitum's oral ampoule format.

Overall validation: Moderate to high. Multiple RCTs, regulatory approvals in over 40 jurisdictions, substantial prescriber experience. Evidence quality is heterogeneous.

Comparison to Cogitum: Cerebrolysin has a neurotrophic peptide mechanism distinct from Cogitum's metabolic substrate mechanism. Cerebrolysin requires parenteral administration; Cogitum is oral. Cerebrolysin has stronger stroke and TBI evidence; Cogitum has stronger asthenic syndrome evidence. Safety profiles are comparable though Cogitum's oral route is more practical for outpatient and pediatric use.

12.3 Cortexin

Mechanism: Polypeptide preparation derived from porcine cerebral cortex; contains a defined mixture of low-molecular-weight neuropeptides, amino acids, vitamins, and minerals. Proposed mechanisms include neurotrophic support, antioxidant activity, and modulation of the balance between excitatory and inhibitory neurotransmission.

Development trajectory: Developed and marketed primarily in Russia and CIS countries for pediatric neurodevelopmental disorders, cerebrovascular disease, traumatic brain injury, and cognitive impairment. Clinical use overlaps substantially with Cogitum in Russian neuropsychiatric practice.

Novelty: Low. The polypeptide preparation approach is conventional within the Russian neurological pharmacotherapy tradition. Mechanistic specificity is limited by the undefined peptide composition.

Effect size: Reported effect sizes in Russian clinical literature suggest moderate cognitive improvement in pediatric populations (comparable to Cogitum). Limited representation in Western indexed journals and in high-impact multicenter trials.

Promising potential: Low to moderate. Clinical use is geographically restricted; no pathway to FDA or EMA approval is evident. Continued use in Russian clinical practice is expected.

Side-effect profile: Well tolerated intramuscularly. Allergic reactions are rare. Requires intramuscular injection (no oral formulation), which is a practical disadvantage relative to Cogitum particularly in pediatric populations.

Overall validation: Low to moderate. Evidence base is concentrated in Russian-language journals with limited international replication.

Comparison to Cogitum: Cortexin shares the Russian neuropsychiatric practice context and overlapping indications with Cogitum. Cogitum has the advantage of oral administration, a defined single active substance with a specific mechanistic rationale, and one Level 1b trial (Esin 2023). Cortexin requires injection and has a less defined mechanism.

12.4 Pantogam (Hopantenic acid)

Mechanism: Calcium salt of D-homopantothenic acid (hopantenic acid); a GABA derivative with combined GABAergic and metabolic (pantothenic acid, vitamin B5 pathway) activity. Proposed mechanisms include enhancement of GABAergic inhibition, metabolic support through the pantothenate pathway, and mild psychostimulant activity.

Development trajectory: Marketed in Russia for cognitive impairment, attention disorders, speech delay, epilepsy-associated cognitive decline, and extrapyramidal disorders. Not available in Western markets. Clinical use overlaps with Cogitum in Russian pediatric neurology.

Novelty: Low. Hopantenic acid is a long-established compound in Russian pharmacology with a conventional GABAergic and metabolic mechanism.

Effect size: Moderate in Russian clinical literature for pediatric cognitive and attentional endpoints. No Western multicenter RCT data are available. Effect sizes appear comparable to Cogitum in similar populations.

Promising potential: Low. Geographically restricted use; no international development pathway. Concern regarding rare hepatotoxicity (Reye-like syndrome reported in Japanese post-marketing surveillance) has limited international adoption.

Side-effect profile: Generally well tolerated. Rare but serious hepatotoxicity (reported in Japan, leading to market withdrawal in that country). This safety concern distinguishes it unfavorably from Cogitum's essentially absent adverse event signal.

Overall validation: Low to moderate. Extensive Russian clinical experience but limited international evidence and a concerning (though rare) hepatotoxicity signal.

Comparison to Cogitum: Pantogam has a GABAergic mechanism distinct from Cogitum's NAA metabolic mechanism. Cogitum has a substantially more favorable safety profile (no hepatotoxicity signal). Both are oral medications used in similar pediatric populations in Russian practice.

12.5 Encephabol (Pyritinol)

Mechanism: Semi-synthetic derivative of pyridoxine (vitamin B6); two pyridoxine molecules linked by a disulfide bridge. Proposed mechanisms include enhancement of cholinergic neurotransmission, neuroprotection through antioxidant activity (glutathione pathway support), and metabolic activation of glucose utilization in brain tissue.

Development trajectory: Developed by Merck KGaA (Germany); marketed in multiple countries (not in the United States) for cognitive impairment in elderly patients, dementia, head trauma sequelae, and pediatric learning disorders. Clinical literature spans several decades with multiple controlled trials.

Novelty: Low. Pyritinol is a long-established compound with a conventional metabolic and cholinergic mechanism.

Effect size: Small to moderate. Controlled trials in dementia and cognitive impairment have demonstrated modest cognitive improvement (Cohen's d approximately 0.2 to 0.3). European registration studies supported approval for cognitive impairment indications.

Promising potential: Low. The compound is mature with declining clinical interest; no significant new development programs are active. Generic competition is established.

Side-effect profile: Generally well tolerated. Reported adverse events include gastrointestinal disturbance, headache, dizziness, and rare autoimmune phenomena (pemphigus-like skin reactions, cholestatic hepatitis). The autoimmune adverse events, though rare, distinguish the safety profile unfavorably from Cogitum.

Overall validation: Moderate. Regulatory approval in multiple countries for cognitive indications; controlled trial evidence; long prescriber experience.

Comparison to Cogitum: Encephabol has a cholinergic and antioxidant mechanism distinct from Cogitum's NAA metabolic mechanism. Both are oral medications approved for cognitive indications. Cogitum has a more favorable safety profile (no autoimmune adverse events). Encephabol has greater international availability and more controlled trial data in elderly cognitive impairment.

12.6 Comparator summary

The five comparators occupy distinct positions in the neurometabolic and nootropic pharmacotherapy landscape. **Piracetam** is the historical prototype nootropic with the largest total evidence base but inconsistent efficacy signals and a non-specific mechanism. **Cerebrolysin** has the strongest controlled trial evidence (stroke, TBI) but requires parenteral administration and has undefined peptide composition. **Cortexin** shares the Russian neuropsychiatric context with Cogitum but requires injection and lacks a defined mechanism. **Pantogam** has a GABAergic mechanism and overlapping pediatric indications but carries a rare hepatotoxicity signal. **Encephabol** has international regulatory approval and controlled trial evidence but rare autoimmune adverse events and declining clinical interest.

Cogitum occupies a distinctive position: it is the only compound in this panel with a specific, defined metabolic substrate mechanism grounded in the established neurobiology of N-acetylaspartate; it has the most favorable safety profile of the group (essentially absent adverse events over five decades of use); it offers a convenient oral formulation suitable for outpatient and pediatric administration; and it has Level 1b evidence from a double-blind placebo-controlled trial for its primary indication (asthenic syndrome). Its principal limitations are the concentration of evidence in Russian-language literature, the absence of large multicenter international trials, and the lack of FDA or EMA evaluation. For research applications requiring a neurometabolic support agent with a defined mechanism, excellent safety, and oral convenience, Cogitum represents a rational selection from the available options.

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