

RESEARCH MONOGRAPH . COMPOUND PROFILE

Phenylpiracetam

A 4-phenyl derivative of piracetam developed at the Russian Institute of Biomedical Problems as a cosmonaut performance enhancer, distinguished from the parent racetam by stereoselective dopamine transporter inhibition, enhanced blood-brain barrier penetration, psychostimulant activity, and a broader pharmacological profile spanning cognition, neuroprotection, cold tolerance, and anti-inflammatory effects.

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ABSTRACT

Phenylpiracetam (fonturacetam, INN; carphedon; 4-phenylpiracetam) is a racetam-class nootropic and psychostimulant first described by Bobkov et al. in 1983 and developed at the Institute of Biomedical Problems of the Russian Academy of Sciences for the enhancement of cognitive, physical, and thermoregulatory performance in cosmonauts operating under conditions of sustained stress, microgravity, and cold exposure. The compound is the 4-phenyl-substituted analog of piracetam and was approved for medical use in Russia in 2003 under the trade name Phenotropil for indications including cerebrovascular insufficiency, cognitive decline following stroke or traumatic brain injury, depression, asthenia, and attentional disorders. Phenylpiracetam is approximately 20- to 60-fold more potent than piracetam in animal models of cognition and anticonvulsant activity, an enhancement attributed to the phenyl substituent conferring increased lipophilicity, improved blood-brain barrier penetration, and direct engagement with monoaminergic and glutamatergic receptor systems that the parent compound does not meaningfully occupy. The molecular pharmacology of phenylpiracetam has been substantially clarified by the work of Zvejniece, Dambrova, and colleagues at the Latvian Institute of Organic Synthesis, who demonstrated in 2011 that the racemic compound binds the α -4- β -2 subtype of the nicotinic acetylcholine receptor with an IC_{50} of 5.86 micromolar, and in 2017 that the individual enantiomers exhibit divergent dopamine transporter (DAT) pharmacology: (R)-phenylpiracetam is a dual norepinephrine-dopamine reuptake inhibitor with an IC_{50} at DAT of approximately 14.5 micromolar and 11-fold lower

affinity for the norepinephrine transporter, while (S)-phenylpiracetam is a selective DAT inhibitor that reduces body weight gain in obese Zucker rats and diet-induced obesity models without producing the locomotor stimulation characteristic of the (R)-enantiomer [1, 2]. The (R)-enantiomer is the more pharmacologically active form for psychostimulant and procognitive effects and is the subject of independent patent filings for Parkinson disease, sleep disorders, and disease-associated fatigue. Both enantiomers additionally modulate AMPA-type glutamate receptors through positive allosteric modulation, consistent with the broader racetam class mechanism, and contribute to neuroprotective and anti-inflammatory activity demonstrated in lipopolysaccharide and carrageenan inflammation models [3]. Pharmacokinetics in humans are characterized by rapid oral absorption with near-complete bioavailability, a time to maximum plasma concentration of approximately one hour, a plasma elimination half-life of three to five hours, and negligible hepatic metabolism: the compound is excreted essentially unchanged, with approximately 40 percent recovered in urine and 60 percent in bile and sweat. The absence of cytochrome P450 involvement eliminates the polymorphic pharmacokinetic variability that complicates other nootropic and psychostimulant agents and reduces drug-drug interaction liability. Clinical evidence is derived predominantly from Russian-language trials of moderate methodological rigor. A 12-month study in approximately 400 post-stroke patients demonstrated enhanced recovery of neurological function and cognitive performance relative to standard rehabilitation. A 30-day trial in 99 patients with cognitive deficits secondary to surgery or traumatic brain injury reported significant improvements in motor coordination,

memory, attention, and higher brain function at 200 mg daily. An adjunctive epilepsy trial reported seizure frequency reduction and cognitive benefit. The compound has been on the World Anti-Doping Agency Prohibited List since 1998 as a stimulant (class S6), following detection in athlete doping control samples at the 1997 World Athletics Championships. This monograph reviews the chemistry, synthesis, and stereochemistry of phenylpiracetam; the dopaminergic, nicotinic, and glutamatergic receptor pharmacology with enantiomer-resolved detail; human pharmacokinetics; the preclinical and clinical evidence base across cognitive, neuroprotective, anti-inflammatory, metabolic, and physical performance domains; sourcing and quality verification; reconstitution and handling; stack-interaction considerations; adverse-event and safety signal; and a comparative assessment of five alternative nootropic and procognitive compounds against phenylpiracetam on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Fonturacetam.

Marketed names: Phenotropil (Valenta Pharm; Russia, discontinued April 2017, reinstated 2022), Nanotropil (alternative Russian formulation, 2018), Actitropil (Russia), Carphedon (common synonym in anti-doping and pharmacological literature), Entrop (Eastern European markets).

Development codes: The compound does not carry a single canonical development code in the Western pharmaceutical development tradition. It is identified in the early Russian literature by the laboratory designation 4-phenylpiracetam and in subsequent pharmacological publications as fonturacetam or carphedon. The designation MRZ-9547 has been applied to (R)-phenylpiracetam specifically in patent filings by Merz Pharmaceuticals [4].

Chemical Abstracts Service registry numbers: 77472-70-9 (racemic free base). The individual enantiomers carry separate registry numbers: (R)-phenylpiracetam (CAS 31252-42-3) and (S)-phenylpiracetam (CAS 31252-43-4). Research-grade material is supplied predominantly as the racemate unless the specific enantiomer is indicated.

International Union of Pure and Applied Chemistry name: 2-(2-oxo-4-phenylpyrrolidin-1-yl)acetamide. The compound is the 4-phenyl derivative of 2-(2-oxopyrrolidin-1-yl)acetamide (piracetam), generated by introduction of a phenyl group at the C-4 position of the gamma-lactam ring.

1.2 Structural class and chemistry

Phenylpiracetam is a 2-pyrrolidone (gamma-lactam) derivative belonging to the racetam structural class, which includes piracetam, aniracetam, oxiracetam, pramiracetam, and levetiracetam. The racetam class is defined by the 2-oxopyrrolidine nucleus linked through the ring nitrogen to an acetamide side chain. Phenylpiracetam is distinguished from the parent compound piracetam by a phenyl substituent at the C-4 position of the pyrrolidone ring, which introduces a

chiral center and confers substantially increased lipophilicity (calculated logP approximately 0.7 for phenylpiracetam versus approximately negative 1.5 for piracetam), improved blood-brain barrier permeability, and direct engagement with monoaminergic receptor systems [5].

Molecular formula: C₁₂H₁₄N₂O₂.

Exact mass: 218.1055 g/mol (monoisotopic).

Molecular weight: 218.25 g/mol.

Physical properties: White to off-white crystalline powder. Soluble in water at moderate concentrations, in dimethyl sulfoxide, in methanol, and in ethanol. Melting point of the racemic form is approximately 130 to 134 degrees Celsius. The compound is stable under standard storage conditions (room temperature, dry, protected from light).

Stereochemistry: Phenylpiracetam contains one stereocenter at C-4 of the pyrrolidone ring and is supplied commercially as the racemic mixture of (R)- and (S)-enantiomers unless otherwise specified. The two enantiomers exhibit markedly different pharmacological profiles. (R)-Phenylpiracetam (also designated (4R)-fonturacetam or MRZ-9547) is the more potent enantiomer for psychostimulant activity, locomotor stimulation, dopamine-norepinephrine reuptake inhibition, and neuroprotection [1, 3]. (S)-Phenylpiracetam is a selective dopamine transporter inhibitor that does not produce locomotor stimulation and has preferential activity in metabolic (anti-obesity) models [2]. Investigators should confirm enantiomeric composition of research-grade material by chiral high-performance liquid chromatography or polarimetry when the stereochemical profile is relevant to the experimental question.

1.3 Synthesis

The synthesis of phenylpiracetam proceeds from commercially available starting materials through two principal routes described in the literature. The first and most direct route involves the alpha-alkylation of piracetam: treatment of piracetam with a strong base (lithium diisopropylamide or sodium hydride in tetrahydrofuran) generates the C-4 enolate, which is trapped with a phenyl electrophile (phenyl halide or phenylboronic acid under transition-metal catalysis) to yield 4-phenylpiracetam as the racemic product [6]. The second route builds the pyrrolidone ring de novo from 4-amino-3-phenylbutyric acid or from alpha-phenyl-

gamma-butyrolactone, proceeding through cyclization and subsequent N-alkylation with chloroacetamide to install the acetamide side chain. A Chinese patent (CN106083685A) describes an optimized route proceeding through 4-phenyl-2-pyrrolidinone with chloroacetamide alkylation, reporting yields of 65 to 80 percent after recrystallization [7]. Resolution of the racemate into individual (R)- and (S)-enantiomers is accomplished by chiral chromatography (preparative chiral HPLC) or by classical resolution with chiral acids (tartaric acid derivatives). Industrial synthesis for the Russian pharmaceutical market was conducted by Valenta Pharm and affiliated contract manufacturers; the specific process chemistry has not been disclosed in the peer-reviewed literature.

2. Abstract

Phenylpiracetam (fonturacetam, carphedon) is a 4-phenyl-substituted derivative of piracetam that exhibits substantially enhanced potency relative to the parent racetam across cognitive, anticonvulsant, and physical performance endpoints in animal and human studies. The compound was first described by Bobkov et al. in 1983 and was developed at the Institute of Biomedical Problems (IBMP) of the Russian (then Soviet) Academy of Sciences for cosmonaut performance support under conditions of prolonged stress, microgravity, and cold exposure [8]. It was approved for medical use in the Russian Federation in 2003 and marketed as Phenotropil (Valenta Pharm) for cerebrovascular insufficiency, post-stroke cognitive rehabilitation, depression, asthenia, and attentional disorders.

The pharmacological profile of phenylpiracetam extends well beyond the positive allosteric modulation of AMPA-type glutamate receptors that defines the racetam class. The compound binds the alpha-4-beta-2 subtype of the nicotinic acetylcholine receptor with an IC₅₀ of 5.86 micromolar, inhibits the dopamine transporter (DAT) with enantiomer-dependent selectivity, and modulates NMDA receptor signaling in cortical and hippocampal circuits [1, 5]. The (R)-enantiomer is a dual norepinephrine-dopamine reuptake inhibitor responsible for the psychostimulant and locomotor-activating properties; the (S)-enantiomer is a selective DAT inhibitor with preferential anti-obesity activity [2, 3]. Both enantiomers contribute to neuroprotective and anti-inflammatory effects demonstrated in models of lipopolysaccharide-induced neuroinflammation and carrageenan-induced peripheral inflammation [3].

Human pharmacokinetics are favorable for a nootropic agent: near-complete oral bioavailability, rapid absorption (time to maximum plasma concentration approximately one hour), a plasma elimination half-life of three to five hours supporting twice-daily dosing, and negligible hepatic metabolism with excretion of the parent compound unchanged [9]. The absence of cytochrome P450 involvement eliminates the pharmacogenomic variability and drug-drug interaction complexity that complicates agents such as modafinil, methylphenidate, and tropisetron.

Clinical evidence derives from a small number of Russian-language trials. A 12-month study in approximately 400 post-stroke patients reported enhanced neurological recovery and cognitive performance [10]. A 30-day trial in 99 patients with surgery- or trauma-related cognitive deficits demonstrated significant improvements in motor coordination, memory, attention, and higher cortical function at 200 mg daily [11]. Adjunctive use in epilepsy reduced seizure frequency and improved cognitive outcomes [12]. The compound is listed by the World Anti-Doping Agency as a prohibited stimulant (class S6, in-competition) since 1998, following detection at the 1997 World Athletics Championships [13].

The compound occupies a distinctive niche in the nootropic and procognitive pharmacology space: it combines the glutamatergic modulation of the racetam class with direct monoaminergic reuptake inhibition, nicotinic receptor engagement, and demonstrated physical performance enhancement, a profile that none of the other marketed racetams or classical nootropic agents replicate. The principal limitation is the quality and scale of the clinical evidence base, which remains dominated by small, predominantly Russian-language trials with limited methodological transparency by international regulatory standards.

3. Discovery and Development History

3.1 Origin and cosmonaut application

Phenylpiracetam was first synthesized and characterized in 1983 by Bobkov and colleagues at the Institute of Biomedical Problems (IBMP) of the Russian (then Soviet) Academy of Sciences, the same institution responsible for biomedical support of the Soviet and Russian space programs [8]. The compound was designed as a more potent derivative of piracetam for use by cosmonauts during extended missions on the Salyut and Mir orbital stations, where sustained cognitive performance, physical endurance, thermoregulation, and resistance to stress-induced fatigue were operational requirements. The addition of the phenyl group to the C-4 position of the piracetam pyrrolidone ring was a deliberate medicinal chemistry modification intended to improve lipophilicity and blood-brain barrier penetration relative to the highly polar parent compound.

Preclinical testing at IBMP and affiliated Soviet research institutions demonstrated that phenylpiracetam was approximately 20- to 60-fold more potent than piracetam in standard rodent models of passive avoidance learning, conditioned avoidance, and anticonvulsant activity (maximal electroshock and pentylenetetrazol seizure models) [5, 14]. The compound additionally demonstrated cold tolerance enhancement (prolonged survival in cold water immersion) and physical endurance effects (increased swimming time to exhaustion) that piracetam did not produce, properties directly relevant to the cosmonaut application.

3.2 Russian pharmaceutical registration

Phenylpiracetam was registered as a pharmaceutical product in the Russian Federation in 2003 under the trade name Phenotropil, manufactured and marketed by Valenta Pharm (Moscow). Approved indications included diseases of the central nervous system of various origins, especially conditions associated with vascular disorders and metabolic disturbances in the brain, including cognitive deficits following stroke and traumatic brain injury; depressive states of mild to moderate severity; psycho-organic syndromes manifesting as intellectual-mnemonic disorders

and apathico-abulic phenomena; convulsive states; obesity of alimentary-constitutional origin; and conditions requiring enhanced resistance to stress and extreme environmental factors [15].

The registered dose was 100 to 300 mg per day in one or two divided doses, with a maximum daily dose of 750 mg. The recommended course of treatment was 30 days, with the possibility of repeated courses.

3.3 Market discontinuation and reinstatement

In April 2017, production of Phenotropil was discontinued following the termination of a licensing agreement between Valenta Pharm and the original rights holders (Valentina and Roman Akhapkin, associated with the IBMP intellectual property) [16]. The discontinuation created a supply gap in the Russian market. The compound was reintroduced as Nanotropil in 2018 and Phenotropil was reinstated in 2022. An alternative formulation, Actitropil (containing fonturacetam), was also registered for similar indications.

3.4 Anti-doping history

Phenylpiracetam (as carphedon) was first detected in athlete doping control samples at the 1997 World Athletics Championships in Athens. The International Olympic Committee added the compound to the Prohibited List in 1998, and it has remained on the World Anti-Doping Agency (WADA) Prohibited List as a stimulant under category S6 (stimulants, prohibited in-competition) since the establishment of the WADA Code in 2003 [13]. Multiple athletes have tested positive for carphedon, including a Russian biathlete at the 2006 Winter Olympics and a Russian cyclist in 2008. The stimulant classification reflects the compound's dopaminergic reuptake inhibition and demonstrated physical performance enhancement, distinguishing it from the unscheduled parent compound piracetam.

3.5 Western pharmaceutical interest

The Latvian Institute of Organic Synthesis (under the direction of Maija Dambrova and Liga Zvejniece) has been the principal Western research group advancing the molecular pharmacology of phenylpiracetam since approximately 2011, producing the enantiomer-resolved DAT binding studies, the neuroprotection and anti-inflammatory characterizations, and the anti-obesity work on (S)-phenylpiracetam [1, 2,

3]. Merz Pharmaceuticals (Frankfurt) has filed patent applications for (R)-phenylpiracetam (designated MRZ-9547) in Parkinson disease, disease-associated fatigue, and sleep disorders, indicating interest in the enantiopure form as a clinical development candidate [4, 17]. As of the date of this monograph, no Western regulatory authority (FDA, EMA, MHRA, TGA) has approved phenylpiracetam or either enantiomer for any indication.

4. Mechanism of Action

Phenylpiracetam is a multi-target ligand. Its principal molecular activities, characterized in heterologous expression systems, native tissue preparations, and behavioral models, are positive allosteric modulation of AMPA-type glutamate receptors, inhibition of the dopamine transporter (with enantiomer-dependent norepinephrine transporter co-inhibition), binding to alpha-4-beta-2 nicotinic acetylcholine receptors, and modulation of NMDA receptor signaling. These activities operate at concentrations achieved by the registered oral dose and contribute differentially to the observed cognitive, psychostimulant, neuroprotective, anti-inflammatory, and thermoregulatory effects.

4.1 AMPA receptor positive allosteric modulation

The racetam class mechanism, shared with piracetam, aniracetam, and other 2-pyrrolidone derivatives, involves positive allosteric modulation (PAM) of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, a major class of ionotropic glutamate receptors mediating fast excitatory synaptic transmission in the cerebral cortex and hippocampus [18]. Piracetam was shown by Ahmed and Oswald (2010) to define a novel allosteric binding site on the AMPA receptor ligand-binding domain distinct from the cyclothiazide and aniracetam sites [19]. Phenylpiracetam retains this mechanism and, through its greater lipophilicity, achieves higher central nervous system concentrations at equivalent oral doses, translating to enhanced AMPA receptor modulation *in vivo*.

The downstream consequences of AMPA receptor potentiation include increased excitatory postsynaptic current amplitude, facilitation of long-term potentiation (LTP) in hippocampal CA1 and CA3 circuits, enhanced brain-derived neurotrophic factor (BDNF) expression, and improved synaptic plasticity. These effects constitute the principal molecular basis for the procognitive and anti-amnesic activity of the racetam class.

4.2 Dopamine transporter inhibition

The Zvejniece laboratory at the Latvian Institute of Organic Synthesis characterized the enantiomer-resolved dopamine transporter pharmacology of phenylpiracetam in a series of publications from 2011 to 2020 [1, 2]. (R)-Phenylpiracetam inhibits dopamine uptake through the dopamine transporter (DAT) with an IC₅₀ of approximately 14.5 micromolar and additionally inhibits the norepinephrine transporter (NET) with approximately 11-fold lower affinity, classifying it as a dual norepinephrine-dopamine reuptake inhibitor (NDRI). (S)-Phenylpiracetam inhibits DAT with approximately 3.5-fold lower potency than the (R)-enantiomer and is selective for DAT over NET and SERT (serotonin transporter), classifying it as a selective DAT inhibitor.

The DAT inhibition is characterized as "atypical" in the sense that (R)-phenylpiracetam does not produce the pronounced locomotor stimulation, stereotypy, or self-administration behavior characteristic of classical DAT inhibitors such as cocaine and methylphenidate at equivalent DAT occupancy [1]. This atypical profile is shared with other slow-onset DAT inhibitors (modafinil, benztropine analogs) and may reflect slow association kinetics, preferential binding to the inward-facing DAT conformation, or differential engagement with DAT-associated intracellular signaling cascades. The distinction is pharmacologically and regulatorily important: atypical DAT inhibitors generally produce lower abuse liability than classical stimulants at equivalent dopamine elevation.

The functional consequences of DAT inhibition include increased extracellular dopamine in the nucleus accumbens, prefrontal cortex, and striatum; increased locomotor activity and exploration (predominantly (R)-enantiomer); enhanced motivation, attention, and working memory through prefrontal dopaminergic facilitation; and the psychostimulant properties that underlie the WADA prohibition.

4.3 Nicotinic acetylcholine receptor binding

Phenylpiracetam binds the alpha-4-beta-2 subtype of the nicotinic acetylcholine receptor (nAChR) in mouse brain cortex homogenates with an IC₅₀ of 5.86 micromolar, as demonstrated by displacement of [3H]-cytisine binding [1]. The functional consequence (agonism, antagonism, or allosteric modulation) has not been fully resolved in electrophysiological studies, though the binding affinity is within the concentration range achieved by the registered oral dose and is consistent with a modulatory rather than primary agonist role. The alpha-4-beta-2 nAChR is the most

abundant nicotinic receptor subtype in the mammalian brain and is the target of nicotine, varenicline, and several cognitive enhancement candidates; engagement of this receptor by phenylpiracetam may contribute to the attentional and working memory enhancement effects observed clinically.

4.4 NMDA receptor modulation

Phenylpiracetam increases the density of NMDA receptors in animal models of chronic administration, an effect reported for the racetam class generally and attributed to upregulation of NR2B-containing NMDA receptor subunits in hippocampal and cortical neurons [5, 20]. The NMDA receptor upregulation may contribute to enhanced synaptic plasticity and LTP induction with chronic dosing. Direct binding of phenylpiracetam to the NMDA receptor complex has not been characterized at the same resolution as the AMPA or DAT interactions, and the NMDA effect may be secondary to the AMPA receptor potentiation or to the dopaminergic modulation of glutamatergic circuits.

4.5 Additional receptor interactions

A broad receptor profiling study cited in the Russian pharmacological literature reports that phenylpiracetam activates or modulates multiple additional receptor systems at micromolar concentrations, including glucagon-like peptide receptors, sphingosine-1-phosphate receptors, peroxisome proliferator-activated receptor gamma (PPAR-gamma), and adenosine receptors, while inhibiting cannabinoid (CB1), opioid, histamine (H1), nociceptin (NOP), orexin (OX1/OX2), and neuropeptide Y (NPY) receptors [15]. The pharmacological significance of these interactions at clinically achieved concentrations is uncertain and has not been independently replicated in Western laboratories. The PPAR-gamma activation, if confirmed, could contribute to the anti-obesity effects of (S)-phenylpiracetam observed in Zucker rat and diet-induced obesity models.

4.6 Composite pharmacology

The composite pharmacology of phenylpiracetam at the registered dose range (100 to 300 mg daily) produces a profile that combines glutamatergic enhancement (AMPA PAM), dopaminergic facilitation (DAT inhibition), cholinergic modulation (alpha-4-beta-2 nAChR binding), and NMDA receptor upregulation. This multi-target engagement distinguishes phenylpiracetam from all other marketed racetams

(piracetam, aniracetam, oxiracetam, pramiracetam), which are primarily or exclusively AMPA receptor modulators without direct monoaminergic activity, and from classical psychostimulants (methylphenidate, amphetamine), which are primarily monoaminergic without glutamatergic modulation.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Phenylpiracetam is rapidly and nearly completely absorbed from the gastrointestinal tract after oral administration. Oral bioavailability is reported as approximately 100 percent in the Russian pharmacokinetic literature [9, 15]. Time to maximum plasma concentration is approximately one hour after oral administration in fasted healthy volunteers. The rapid absorption is consistent with the compound's moderate lipophilicity (logP approximately 0.7), molecular weight (218.25 g/mol), and lack of ionizable groups at physiological pH.

5.2 Distribution

Phenylpiracetam distributes rapidly to tissues after absorption. The compound crosses the blood-brain barrier readily, a property attributed to the phenyl substituent conferring increased lipophilicity relative to piracetam (which crosses the blood-brain barrier poorly and slowly). Central nervous system penetration has been confirmed in animal models by measurement of brain-to-plasma concentration ratios and by the rapid onset of central pharmacological effects (locomotor activation, anticonvulsant activity) within 20 to 30 minutes of intraperitoneal administration in rodents. Specific volume of distribution and plasma protein binding values have not been reported in the peer-reviewed literature with the precision typical of Western regulatory submissions.

5.3 Metabolism

Phenylpiracetam is not significantly metabolized in humans. The compound is excreted essentially unchanged, indicating minimal hepatic biotransformation [9, 15]. This pharmacokinetic property is shared with piracetam and levetiracetam and reflects the metabolic stability of the 2-pyrrolidone ring system and the absence of readily oxidizable functional groups. The absence of cytochrome P450 involvement has two important practical consequences: (a) there is no pharmacogenomic vari-

ability in elimination related to CYP2D6, CYP2C19, CYP3A4, or other polymorphic enzymes, eliminating the inter-individual dose-response variability that complicates modafinil, methylphenidate, and many other psychoactive agents; and (b) drug-drug interaction liability through CYP inhibition or induction is negligible.

5.4 Elimination

Phenylpiracetam is eliminated by renal and biliary excretion of the unchanged parent compound. Approximately 40 percent of an administered dose is recovered in urine and approximately 60 percent in bile and sweat [9]. The plasma elimination half-life is three to five hours, supporting once- or twice-daily dosing for sustained cognitive effects and permitting evening clearance to minimize sleep disruption when the compound is taken in the morning or early afternoon.

5.5 Routes of administration

The registered route of administration is oral. Phenylpiracetam is supplied as 100 mg tablets (Phenotropil) or 100 mg capsules (Actitropil). The compound is water-soluble and could in principle be administered by other routes (sublingual, intravenous), but non-oral routes are not registered and have not been characterized in published human pharmacokinetic studies. Research-grade material is supplied as a crystalline powder suitable for dissolution in aqueous or DMSO vehicles for in vitro and animal studies.

5.6 Special populations

Pediatric, geriatric, renal impairment, and hepatic impairment pharmacokinetic data have not been published in the peer-reviewed literature to Western regulatory standards. The Russian prescribing information recommends caution in severe hepatic and renal impairment and does not recommend use in children under 18 years of age or in pregnant or lactating women owing to insufficient safety data.

6. Preclinical Pharmacology

6.1 Cognition and antiamnesic effects

Phenylpiracetam improves learning and memory in multiple rodent paradigms including passive avoidance, active avoidance, Morris water maze, novel object recognition, and radial arm maze [5, 14]. The compound is consistently 20- to 60-fold more potent than piracetam in these assays, with effective doses in the range of 1 to 50 mg/kg intraperitoneally compared to 100 to 500 mg/kg for piracetam. The anti-amnesic effect is demonstrated against scopolamine-induced amnesia (cholinergic blockade model), electroconvulsive shock-induced amnesia, and hypoxia-induced cognitive deficit.

6.2 Anticonvulsant activity

Phenylpiracetam demonstrates anticonvulsant properties in the maximal electroshock seizure test and the pentylenetetrazol seizure threshold test in mice and rats [14]. The anticonvulsant potency exceeds that of piracetam and approaches that of levetiracetam in some models. The anticonvulsant mechanism is attributed to the combined AMPA receptor modulation and GABAergic enhancement, though direct GABA receptor binding has not been convincingly demonstrated. Lybzikova et al. (2008) reported adjunctive benefit in a small clinical epilepsy cohort [12].

6.3 Neuroprotection

In models of cerebral ischemia (middle cerebral artery occlusion in rats), phenylpiracetam reduces infarct volume, improves neurological deficit scores, and enhances recovery of cognitive function compared to vehicle-treated animals and to piracetam at equivalent doses [5, 10]. Zvejniece et al. (2020) demonstrated that (R)-phenylpiracetam attenuated lipopolysaccharide (LPS)-induced body temperature reduction and reduced the overexpression of inflammatory genes including tumor necrosis factor alpha (TNF-alpha), interleukin-1 beta (IL-1-beta), and inducible nitric oxide synthase (iNOS) in a mouse neuroinflammation model [3]. Seven-day

oral pretreatment with (R)-phenylpiracetam dose-dependently reduced paw edema in carrageenan-induced inflammation and reduced the nociceptive response during the inflammatory phase of formalin-induced pain tests.

6.4 Cold tolerance and physical endurance

The cosmonaut application of phenylpiracetam was predicated on enhanced cold tolerance and physical endurance. In cold-water immersion survival models in rodents, phenylpiracetam prolonged survival time significantly compared to vehicle and to piracetam [8]. In forced swimming tests, the compound increased swimming time to exhaustion, an effect attributed to a combination of dopaminergic stimulation, enhanced thermoregulation, and reduced perception of fatigue. These properties distinguish phenylpiracetam from all other marketed racetams and are the basis for the WADA stimulant classification.

6.5 Anti-obesity effects

Zvejniece et al. (2017) demonstrated that (S)-phenylpiracetam, administered to genetically obese Zucker rats and to mice on a Western-type high-fat diet, significantly decreased body weight gain and fat mass accumulation without producing the locomotor stimulation characteristic of classical anorexigenic stimulants [2]. The anti-obesity effect was attributed to selective DAT inhibition modulating mesolimbic reward circuits and feeding behavior. The (R)-enantiomer did not produce equivalent weight reduction at doses that stimulated locomotor activity, suggesting that the anti-obesity and psychostimulant effects are dissociable through enantioselective pharmacology.

7. Clinical Evidence Base

7.1 Post-stroke cognitive rehabilitation

The largest published clinical study of phenylpiracetam enrolled approximately 400 patients with ischemic stroke and followed them for 12 months during standard rehabilitation supplemented with phenylpiracetam at 100 to 200 mg daily [10]. The study, conducted at Russian rehabilitation centers and published in Russian-language clinical journals, reported significant improvement in neurological deficit scores, cognitive test performance (attention, memory, executive function), and functional recovery compared to rehabilitation alone. The methodological details (randomization procedure, blinding, statistical analysis plan) available in the published report do not meet the standards of contemporary Western clinical trial registration and reporting (CONSORT), and the study should be interpreted accordingly.

7.2 Cognitive deficits following surgery and traumatic brain injury

A 30-day trial in 99 adults aged 40 to 60 years with cognitive deficits secondary to surgical procedures or traumatic brain injury reported significant improvements in motor coordination, memory, attention, and higher brain function after treatment with phenylpiracetam 200 mg daily compared to baseline [11]. The effect sizes were clinically meaningful by the investigators' assessment, with improvement across multiple cognitive domains.

7.3 Epilepsy

Lybzikova et al. (2008) investigated phenylpiracetam as adjunctive therapy in patients with epilepsy complicated by cognitive impairment [12]. The compound reduced seizure frequency and produced dual benefit of seizure reduction and cognitive improvement, with the latter attributed to the procognitive mechanism independent of the anticonvulsant effect. The study was small and should be regarded as hypothesis-generating.

7.4 Cerebrovascular insufficiency and chronic fatigue

The registered Russian indications include cerebrovascular insufficiency with associated cognitive decline, psycho-organic syndromes, asthenia, and depressive states of mild to moderate severity [15]. The clinical evidence supporting these indications is derived from the registration dossier submitted to Russian regulatory authorities and from post-marketing observational studies published in Russian clinical journals. The data have not been subjected to independent systematic review or meta-analysis to international standards.

7.5 Physical and cognitive performance in healthy individuals

Anecdotal and observational reports from the cosmonaut program and from the broader nootropic user community describe enhanced focus, motivation, physical stamina, and cold tolerance in healthy individuals at doses of 100 to 200 mg [8, 13]. Controlled clinical trials in healthy volunteers have not been published in the indexed peer-reviewed literature, and the performance-enhancement evidence in healthy populations is therefore informal.

7.6 Limitations of the clinical evidence

The clinical evidence base for phenylpiracetam is substantially smaller and methodologically weaker than that available for established cognitive enhancement agents (donepezil, memantine, methylphenidate, modafinil) or for comparator racetams with Western clinical development (levetiracetam for epilepsy, piracetam for myoclonus). The published trials are predominantly Russian-language, small in sample size, and incompletely reported by international standards. No randomized controlled trial of phenylpiracetam has been registered on ClinicalTrials.gov or conducted under an FDA or EMA Investigational New Drug application. The compound should therefore be regarded as having promising pre-clinical and pilot clinical support but lacking the definitive large-scale, placebo-controlled, adequately powered clinical trial evidence required for Western regulatory registration.

8. Sourcing and Quality Verification

Pharmaceutical-grade phenylpiracetam (Phenotropil, Actitropil, Nanotropil) is available through Russian pharmacy supply chains and through international pharmacy forwarding services that handle Russian-registered pharmaceuticals. The pharmaceutical material is supplied as 100 mg tablets or capsules. Investigators outside Russia should confirm that importation complies with local regulatory requirements for pharmaceutical research materials.

Research-grade phenylpiracetam is supplied by multiple chemical and pharmaceutical research suppliers (MedChemExpress, Cayman Chemical, TCI America, Sigma-Aldrich, Tocris, GlpBio, BocSci, and others) at greater than 98 percent purity by HPLC. Supply is in milligram to gram quantities as the racemic free base. Individual enantiomers ((R)-phenylpiracetam and (S)-phenylpiracetam) are available from selected suppliers at research-grade purity but at substantially higher cost. Pricing for racemic material is moderate, in the range of \$30 to \$150 per gram at the time of monograph preparation.

Investigators should confirm compound identity and purity on every research-grade lot through:

- High-performance liquid chromatography area-percent purity, ideally greater than 98 percent
- Mass spectrometry confirmation of molecular weight (219.1128 for the protonated species $[M+H]^+$)
- Chiral HPLC or polarimetry if enantiomeric composition is relevant to the study design
- Nuclear magnetic resonance spectroscopy (1H and ^{13}C) for structural confirmation
- Karl Fischer or loss-on-drying analysis for residual water content
- Residual solvent analysis by gas chromatography

Third-party analytical laboratories provide independent confirmation of vendor certificates of analysis. The research-grade phenylpiracetam market is well established; however, given the compound's popularity in the nootropic supplement market, adulteration or substitution in consumer-grade (non-pharmaceutical, non-

research) sources is a recognized concern. Investigators should acquire material only from established chemical suppliers with documented quality management systems.

9. Reconstitution and Handling

Phenylpiracetam is supplied as a white crystalline powder that is soluble in water at concentrations suitable for in vivo dosing. For in vitro research, stock solutions are typically prepared at 10 to 100 mM in dimethyl sulfoxide (DMSO), sterile-filtered, aliquoted, and stored at minus 20 degrees Celsius. Aqueous stock solutions for in vivo administration are prepared in normal saline or phosphate-buffered saline at concentrations of 1 to 50 mg/mL and should be used within 24 hours of preparation or within 7 days if stored at 2 to 8 degrees Celsius.

Storage of the solid is appropriate at room temperature (15 to 25 degrees Celsius) in a dry, light-protected container. The compound is stable under these conditions for at least 24 months from the date of manufacture based on accelerated stability data. Refrigerated storage (2 to 8 degrees Celsius) extends shelf life and is recommended for long-term archival of research-grade material.

For oral administration in animal studies, the compound may be dissolved in water or suspended in 0.5 percent carboxymethylcellulose and administered by oral gavage. For intraperitoneal administration, dissolution in warm normal saline with brief sonication is sufficient for most dose ranges.

Aliquoting of DMSO stock solutions for single-use is recommended to minimize freeze-thaw degradation. The compound demonstrates adequate stability through at least three freeze-thaw cycles without measurable loss of potency by HPLC.

10. Stack Interactions and Combinations

Phenylpiracetam interacts with several compound classes through its multi-target pharmacology. Investigators conducting research with phenylpiracetam, particularly in combination protocols or in subjects taking concurrent medications, should consider:

Dopaminergic agents: Concurrent use with other dopamine reuptake inhibitors (methylphenidate, bupropion, modafinil) or dopamine releasing agents (amphetamine, lisdexamfetamine) produces additive or synergistic dopaminergic stimulation, with increased risk of overstimulation, insomnia, anxiety, tachycardia, and hypertension. The combination is not recommended without careful dose titration and monitoring.

Cholinergic agents: Concurrent acetylcholinesterase inhibitors (donepezil, rivastigmine, galantamine) or choline precursors (alpha-GPC, citicoline) produce additive cholinergic activity through complementary mechanisms (increased acetylcholine availability combined with nicotinic receptor modulation). The combination has a plausible pharmacological rationale for enhanced cognitive effects, though clinical evidence for the combination is absent.

Other racetams: Concurrent piracetam, aniracetam, or oxiracetam is pharmacologically redundant at the AMPA receptor level and may produce additive glutamatergic stimulation. The combination has no clinical evidence of synergistic benefit over phenylpiracetam alone.

Caffeine and other xanthines: Concurrent caffeine produces additive psychostimulant effects through complementary mechanisms (adenosine receptor antagonism combined with dopamine reuptake inhibition). The combination may increase the risk of anxiety, insomnia, and cardiovascular stimulation (tachycardia, hypertension) in susceptible individuals.

GABAergic agents: Concurrent benzodiazepines, Z-drugs (zolpidem, zopiclone), or alcohol may have their sedative effects partially counteracted by phenylpiracetam, consistent with the anticonvulsant interaction literature reporting that

phenylpiracetam weakens the sedative effect of benzodiazepines [14]. Conversely, GABAergic agents may blunt the procognitive and stimulant effects of phenylpiracetam.

Levodopa and dopamine agonists: In the context of Parkinson disease research (for which (R)-phenylpiracetam has been patented), concurrent levodopa or dopamine agonists (pramipexole, ropinirole) would produce additive dopaminergic stimulation. The combination may have therapeutic potential but has not been studied in clinical trials.

CYP-metabolized agents: Because phenylpiracetam does not undergo CYP metabolism and does not inhibit or induce CYP enzymes, pharmacokinetic drug-drug interactions through the CYP system are not expected. This is a practical advantage over many other psychoactive agents.

11. Adverse Events and Safety

11.1 Common adverse events

The adverse-event profile at registered doses (100 to 300 mg daily) as reported in the Russian prescribing information and in published clinical studies includes:

- Insomnia (5 to 10 percent, dose-dependent; attributed to dopaminergic stimulation and recommended to be managed by avoiding evening dosing)
- Psychomotor agitation (3 to 5 percent at higher doses)
- Headache (2 to 5 percent)
- Nausea (1 to 3 percent)
- Elevated blood pressure (transient, 1 to 3 percent)
- Skin flushing and warmth (1 to 2 percent)

These adverse events are generally mild, dose-dependent, and resolve with dose reduction or discontinuation. Tolerance to the psychostimulant effects has been reported with chronic daily use, though formal tolerance studies have not been published.

11.2 Rare and serious adverse events

No serious adverse events have been reported in the published clinical literature at registered doses. The Russian prescribing information does not list life-threatening events in the adverse-event section. However, the clinical evidence base is small relative to widely used psychostimulants, and rare events may not have been captured. Theoretical concerns based on the pharmacological profile include:

- Psychosis or mania in predisposed individuals (dopaminergic mechanism, by analogy with other stimulants)
- Seizure provocation at supratherapeutic doses (AMPA receptor potentiation, though the compound demonstrates anticonvulsant rather than proconvulsant activity at studied doses)
- Cardiovascular events (tachycardia, hypertension) at high doses or in combination with other stimulants

11.3 Tolerance and dependence

Anecdotal reports describe tolerance to the psychostimulant effects of phenylpiracetam with daily use over periods of one to two weeks, necessitating intermittent (cycling) dosing schedules for maintained effect [13]. The atypical DAT inhibitor profile suggests lower abuse liability than classical stimulants, but formal abuse liability studies (self-administration, drug discrimination, withdrawal characterization) have not been published. The Russian prescribing information recommends courses of 30 days with breaks between courses, a practice that may reflect awareness of tolerance.

11.4 Pregnancy and lactation

There are insufficient human data to evaluate the safety of phenylpiracetam during pregnancy or lactation. Animal teratogenicity data have not been published in the indexed peer-reviewed literature. The Russian prescribing information contraindicates use in pregnancy and lactation.

11.5 Contraindications

The Russian prescribing information lists hypersensitivity to the compound or excipients as the primary contraindication. Caution is recommended in patients with severe hepatic or renal impairment and in patients with a history of psychosis or severe anxiety disorders.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five nootropic and procognitive compounds against phenylpiracetam, evaluated against 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 the principal compounds that share meaningful pharmacological overlap with phenylpiracetam or occupy the same competitive niche in cognitive enhancement research.

12.1 Piracetam

Mechanism: Positive allosteric modulator of AMPA receptors. The parent compound of the racetam class and the prototype nootropic agent, first synthesized by UCB Pharma in the 1960s. Piracetam has no significant monoaminergic activity and crosses the blood-brain barrier poorly owing to high polarity [18].

Development trajectory: Piracetam has been studied in hundreds of clinical trials across indications including myoclonus, cognitive decline in dementia, post-stroke aphasia, vertigo, and sickle cell disease. It is approved as a medicine in many European jurisdictions (brand name Nootropil) and is available without prescription in some countries.

Novelty: Low. Piracetam is the oldest and most extensively studied racetam and the benchmark against which all subsequent racetam derivatives are compared.

Effect size: Meta-analyses of piracetam in cognitive impairment (Waegemans et al. 2002) report small but statistically significant effect sizes (Cohen's d approximately 0.15 to 0.3) on global cognitive measures in patients with dementia or cognitive decline [21]. Effect sizes in healthy volunteers are not consistently significant. Piracetam is approximately 20- to 60-fold less potent than phenylpiracetam in animal cognitive models.

Promising potential: Moderate. The compound has decades of clinical use and a well-established safety profile but has not achieved regulatory approval in the United States and faces the limitation of small effect sizes in adequately powered trials.

Side-effect profile: Favorable. Piracetam is well tolerated at doses up to 24 g/day in clinical studies, with the principal adverse events being gastrointestinal discomfort and headache. No serious adverse events are attributable to the compound at clinical doses.

Overall validation: Moderate to high. The clinical evidence base is extensive, though effect sizes are modest. The compound serves as the reference standard for the racetam class.

Comparison to phenylpiracetam: Piracetam is substantially less potent than phenylpiracetam in animal and human cognitive endpoints, lacks the monoaminergic activity that confers psychostimulant and motivational enhancement, and does not cross the blood-brain barrier as efficiently. Phenylpiracetam offers a more potent and broader pharmacological profile but with a substantially weaker clinical evidence base. Piracetam has the advantage of decades of safety data and international regulatory acceptance for specific indications.

12.2 Modafinil

Mechanism: Weak DAT inhibitor with additional effects on orexinergic, histaminergic, and glutamatergic neurotransmission. The precise mechanism of the wakefulness-promoting effect remains incompletely characterized despite extensive study [22].

Development trajectory: Modafinil was developed by Laboratoire Lafon (France) and approved by the FDA in 1998 for narcolepsy, later extended to shift work sleep disorder and obstructive sleep apnea-related excessive daytime sleepiness. It is widely used off-label for cognitive enhancement, fatigue management, and ADHD.

Novelty: Moderate. Modafinil was the first clinically approved wakefulness-promoting agent with a non-amphetamine mechanism, though subsequent research has identified DAT inhibition as the primary mechanism.

Effect size: Moderate. Controlled trials demonstrate significant improvement on tests of attention, executive function, and working memory in sleep-deprived and narcoleptic populations. Effect sizes in well-rested healthy volunteers are small and inconsistent [23]. The cognitive-enhancing profile is narrower than that of phenylpiracetam (primarily wakefulness and attention rather than memory and learning).

Promising potential: High. Modafinil is FDA-approved, extensively prescribed, and the subject of a large and continuing research literature. The compound is well established as the standard of care for narcolepsy and as the primary reference compound for cognitive-enhancing stimulants.

Side-effect profile: Moderate. Headache (15 to 20 percent), nausea (5 to 10 percent), insomnia (5 percent), anxiety, and rare serious skin reactions (Stevens-Johnson syndrome, reported at approximately 1 in 100,000 exposures). CYP3A4 induction produces significant drug-drug interactions with oral contraceptives and other CYP3A4 substrates.

Overall validation: High. Extensive clinical evidence from registration-quality trials, FDA approval, and decades of postmarketing experience.

Comparison to phenylpiracetam: Modafinil and phenylpiracetam share DAT inhibition as a mechanism but diverge in pharmacological breadth (phenylpiracetam adds AMPA modulation, nicotinic binding, and NMDA upregulation), in potency at DAT (similar), and in clinical evidence (modafinil vastly superior). Modafinil has CYP-mediated metabolism with associated drug-drug interactions; phenylpiracetam does not. Phenylpiracetam offers broader pharmacological activity and absence of CYP interactions; modafinil offers vastly superior clinical validation and regulatory status.

12.3 Pramiracetam

Mechanism: High-affinity choline uptake enhancer and AMPA receptor positive allosteric modulator. Pramiracetam is a racetam derivative distinguished by a dipropan-2-ylaminoethyl substituent on the acetamide nitrogen, conferring high lipophilicity and enhanced CNS penetration relative to piracetam [24].

Development trajectory: Pramiracetam was developed by Parke-Davis and advanced through clinical trials in Alzheimer's disease and traumatic brain injury in the 1990s. It is marketed in some European countries (brand name Pramistar) for

cognitive impairment. It has not achieved FDA approval.

Novelty: Low to moderate. The mechanism is an extension of the racetam class with enhanced cholinergic facilitation.

Effect size: Moderate in traumatic brain injury studies; a small controlled trial reported significant improvement in memory and orientation compared to piracetam in TBI patients [25]. Effect sizes in other populations are not well characterized.

Promising potential: Low. The compound is no longer in active development and has limited clinical momentum. Research-grade material is available.

Side-effect profile: Favorable. Well tolerated at studied doses (600 to 1200 mg daily). Headache and gastrointestinal discomfort are the principal adverse events.

Overall validation: Low to moderate. Limited clinical evidence, though the TBI data are positive.

Comparison to phenylpiracetam: Pramiracetam and phenylpiracetam are both lipophilic racetam derivatives with enhanced CNS penetration relative to piracetam. Pramiracetam acts primarily through cholinergic facilitation; phenylpiracetam acts primarily through dopaminergic and glutamatergic mechanisms. Phenylpiracetam offers broader pharmacological activity and psychostimulant properties that pramiracetam lacks. Clinical evidence is modest for both compounds.

12.4 Noopept (GVS-111, omberacetam)

Mechanism: Dipeptide analog that is metabolized to cycloprolylglycine and modulates AMPA and NMDA receptors, increases BDNF and NGF expression, and enhances cholinergic neurotransmission. Despite structural similarity to the racetam class, noopept is technically a peptide-derived nootropic with a distinct binding profile [26].

Development trajectory: Developed at the Institute of Pharmacology of the Russian Academy of Medical Sciences. Approved in Russia for cognitive impairment. It has not been approved by Western regulatory authorities.

Novelty: Moderate. The peptide-based mechanism and the BDNF/NGF induction distinguish noopept from classical racetams.

Effect size: Noopept is reported as approximately 1000-fold more potent than piracetam by weight in animal models of anti-amnesic activity, reflecting both the higher receptor affinity and the lower molecular weight [26]. Human clinical evidence is limited to Russian trials of moderate methodological quality.

Promising potential: Low to moderate. Similar to phenylpiracetam, the compound is approved in Russia but lacks Western regulatory acceptance.

Side-effect profile: Favorable at studied doses (10 to 30 mg daily). Adverse events are mild and infrequent.

Overall validation: Low to moderate. Predominantly Russian clinical evidence with limited international replication.

Comparison to phenylpiracetam: Noopept and phenylpiracetam share the Russian development history, the regulatory status (approved in Russia, not in Western jurisdictions), and the limited clinical evidence base. Noopept is substantially more potent by weight and acts through neurotrophic (BDNF, NGF) mechanisms that phenylpiracetam does not prominently engage. Phenylpiracetam offers psychostimulant and physical performance effects that noopept lacks. The two compounds are complementary rather than competitive.

12.5 Fasoracetam (NS-105, NFC-1)

Mechanism: Racetam derivative that acts as a high-affinity agonist at metabotropic glutamate receptors (mGluR2/3), upregulates GABA-B receptors, and modulates cholinergic neurotransmission [27]. The metabotropic glutamate receptor mechanism is distinct from the ionotropic (AMPA/NMDA) modulation of other racetams.

Development trajectory: Originally developed by Nippon Shinyaku for dementia indications and advanced through Phase 3 clinical trials in Japan in the 1990s, which failed to demonstrate efficacy. The compound was subsequently acquired by Aevi Technologies (now Aevi Genomic Medicine) and repositioned for ADHD in adolescents with mutations in mGluR network genes, producing positive results in a small open-label trial [28]. The ADHD development program has not produced a registration trial.

Novelty: High. The mGluR and GABA-B receptor upregulation mechanism is mechanistically distinct from all other racetams and from the dopaminergic mechanism of phenylpiracetam.

Effect size: Phase 3 failure in dementia suggests insufficient effect size for that indication. The ADHD signal in genetically selected patients is interesting but preliminary.

Promising potential: Low to moderate. Development is dormant for the original dementia indication. The genetically stratified ADHD approach is novel but early-stage.

Side-effect profile: Favorable. Well tolerated at studied doses in Phase 1 through Phase 3 trials.

Overall validation: Low. Phase 3 failure in the primary indication.

Comparison to phenylpiracetam: Fasoracetam and phenylpiracetam are mechanistically distinct (metabotropic glutamate versus ionotropic glutamate plus dopaminergic). Fasoracetam has a more advanced Western clinical development history (Phase 3, though failed) but lower overall pharmacological potency as a cognitive enhancer. Phenylpiracetam offers broader pharmacological activity and psychostimulant properties. The two compounds address different receptor systems and could theoretically be complementary.

12.6 Comparator summary

The five comparators occupy distinct positions in the nootropic and cognitive enhancement space. **Piracetam** is the prototype racetam with extensive clinical history but modest effect sizes and no monoaminergic activity. **Modafinil** is the most clinically validated wakefulness-promoting agent with DAT inhibition, but narrower pharmacological breadth than phenylpiracetam and significant CYP interactions. **Pramiracetam** is a lipophilic racetam with cholinergic facilitation but limited clinical data and no stimulant properties. **Noopept** is a highly potent peptide-derived nootropic with neurotrophic mechanisms, sharing phenylpiracetam's Russian regulatory status and evidence-base limitations. **Fasoracetam** offers a novel metabotropic glutamate receptor mechanism but has failed in Phase 3 for its primary indication.

Phenylpiracetam occupies a unique position: it is the only compound in this comparator panel that combines glutamatergic modulation (AMPA PAM), direct monoaminergic reuptake inhibition (DAT, NET), nicotinic receptor engagement, demonstrated physical performance and cold tolerance enhancement, and a registered pharmaceutical indication (in Russia). Its principal limitations are the quality

and scale of the clinical evidence base and the absence of Western regulatory approval. The enantiomer-resolved pharmacology (Zvejniece and Dambrova, 2017 to 2020) opens a path toward enantiopure clinical development that could address the evidence-base limitation through conventional Western regulatory mechanisms, as indicated by the Merz Pharmaceuticals patent filings for (R)-phenylpiracetam.

Investigators considering phenylpiracetam for cognitive, neuroprotective, or performance enhancement research should expect a pharmacologically potent and multi-target compound with favorable pharmacokinetics, a promising but under-validated clinical profile, and a distinctive combination of procognitive and psychostimulant activity that is not replicated by any other racetam or any single comparator agent.

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