

RESEARCH MONOGRAPH . COMPOUND PROFILE

Nefiracetam

A lipophilic 2-oxopyrrolidinyl acetamide derived from the piracetam scaffold, developed by Daiichi Pharmaceutical as an anti-amnesic agent for cerebrovascular dementia and distinguished from other racetams by concurrent modulation of GABA-A receptors, neuronal nicotinic acetylcholine receptors, voltage-gated calcium channels, and NMDA receptor function through convergent protein kinase C and CaM kinase II signaling.

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ABSTRACT

Nefiracetam (DM-9384, Translon), the N-(2,6-dimethylphenyl) acetamide derivative of 2-oxopyrrolidine and the most pharmacologically characterized fat-soluble member of the racetam nootropic class, is a cognition-enhancing agent developed by Daiichi Pharmaceutical (now Daiichi Sankyo) in Japan during the 1980s for the treatment of cognitive impairment secondary to cerebrovascular disease. Unlike the parent compound piracetam, which acts principally through membrane fluidity modulation and non-specific cholinergic facilitation, nefiracetam engages a convergent set of molecular targets: high-affinity interaction with the GABA-A receptor chloride channel complex (IC₅₀ approximately 8.5 nM for displacement of [³H]muscimol binding), potentiation of neuronal nicotinic acetylcholine receptor currents through a G-protein-coupled protein kinase C pathway, enhancement of voltage-gated L-type and N-type calcium channel currents, potentiation of NMDA receptor function via protein kinase C activation with consequent reduction of the voltage-dependent magnesium block, and facilitation of hippocampal long-term potentiation through CaM kinase II and protein kinase C alpha activation downstream of NMDA receptor and metabotropic glutamate receptor 5 stimulation. The composite pharmacology produces a sustained facilitation of hippocampal synaptic transmission that resembles long-term potentiation and that depends on presynaptic nicotinic acetylcholine receptor activation and consequent glutamate release.

Pharmacokinetics in healthy human volunteers are characterized by rapid oral absorption with peak plasma concentrations at

approximately 1 to 2 hours, monophasic elimination with a plasma half-life of 3 to 5 hours, linear dose-proportional kinetics across the 100 to 900 mg range, negligible accumulation on repeated dosing, and principal hepatic metabolism through CYP3A4-mediated 5-hydroxylation of the pyrrolidine ring with a minor contribution from CYP1A2. Less than 10 percent of the administered dose is excreted unchanged in urine. The compound crosses the blood-brain barrier readily owing to its lipophilicity relative to piracetam.

The clinical development program encompassed three principal indications. In cerebrovascular dementia, Phase 2 and Phase 3 trials conducted in Japan by Daiichi demonstrated cognitive improvement in patients with sequelae of cerebral infarction; however, a revised Phase 3 trial failed to meet its primary endpoint, and the New Drug Application was withdrawn in Japan in February 2002. In Alzheimer's disease, the National Institute of Neurological Disorders and Stroke sponsored a randomized, double-blind, placebo-controlled Phase 2 trial (NCT00001933) evaluating nefiracetam at 600 mg and 900 mg daily for 20 weeks; preliminary reports indicated dose-dependent cognitive improvement in a subset of patients, but the program was not advanced to Phase 3. In poststroke depression and apathy, Robinson et al. (2008, 2009) conducted randomized controlled trials demonstrating that nefiracetam at 900 mg daily produced significant reduction in apathy scores in poststroke depressed patients, though the primary depression endpoint was not met; a subsequent confirmatory trial by Starkstein et al. (2016) for poststroke apathy did not replicate the benefit, possibly owing to insufficient statistical power.

The compound is not approved in any jurisdiction as of the current monograph date. It is available as a research-grade preparation from multiple chemical suppliers. The principal preclinical toxicology concern is species-specific nephrotoxicity observed in dogs and rats attributable to a metabolite (M-18) that is not formed in humans or primates; long-term studies in humans and primates have not identified renal toxicity. This monograph reviews the chemistry, synthesis, and structural positioning of nefiracetam; the multi-target molecular pharmacology in mechanistic detail; the human pharmacokinetic record; the preclinical pharmacology across cognitive, anticonvulsant, and neuroprotective models; the clinical evidence base across all studied indications; sourcing and quality verification; reconstitution and handling; stack-interaction considerations; adverse-event and safety signal; and a structured comparative assessment of five racetam-class nootropics against nefiracetam on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Nefiracetam.

Marketed name: Translon (Daiichi Pharmaceutical; Japan, development stage only; not commercially launched).

Development codes: DM-9384 (Daiichi Pharmaceutical). The development code DM-9384 is the canonical identifier in the early Japanese pharmacology literature and in the principal preclinical characterization papers from the Nishizaki and Yoshii laboratories [1, 2]. Additional codes used in regulatory filings include DZL-221.

Chemical Abstracts Service registry number: 77191-36-7.

PubChem compound identifier: CID 71157.

DrugBank identifier: DB13082.

International Union of Pure and Applied Chemistry name: N-(2,6-dimethylphenyl)-2-(2-oxopyrrolidin-1-yl)acetamide. The compound is the N-(2,6-dimethylphenyl)acetamide derivative of 2-pyrrolidinone (gamma-butyrolactam), placing it within the 2-oxopyrrolidine acetamide structural family that includes piracetam, aniracetam, and oxiracetam.

1.2 Structural class and chemistry

Nefiracetam is a fat-soluble pyrrolidinone-type racetam nootropic. The structural class places it within the 2-oxopyrrolidine (gamma-butyrolactam) family of cognitive enhancers derived from the piracetam scaffold. The key structural modification relative to piracetam is the replacement of the terminal primary amide with an N-(2,6-dimethylphenyl)acetamide group, which substantially increases lipophilicity, molecular weight, and blood-brain barrier penetration relative to the parent compound [3].

Molecular formula: C₁₄H₁₈N₂O₂.

Molecular weight: 246.31 g/mol.

Exact mass: 246.1368 g/mol (monoisotopic).

Physical properties: White to off-white crystalline powder. Soluble in dimethyl sulfoxide, ethanol, and methanol; sparingly soluble in water. Melting point approximately 151 to 153 degrees Celsius. The compound is lipophilic relative to piracetam; the increased lipophilicity is attributable to the 2,6-dimethylphenyl substituent and is the principal structural basis for improved oral bioavailability and central nervous system penetration.

Stereochemistry: Nefiracetam does not contain a chiral center in its standard form. The pyrrolidine ring is achiral at the point of nitrogen attachment. However, the principal metabolite 5-hydroxynefiracetam (5-OHN) introduces a stereocenter at the 5-position of the pyrrolidine ring, and the hydroxylation is stereoselective in humans, producing predominantly the (S)-5-hydroxy enantiomer [4].

1.3 Synthesis

The published synthesis of nefiracetam proceeds through condensation of 2-pyrrolidinone with chloroacetyl chloride to produce 2-(2-oxopyrrolidin-1-yl)acetyl chloride, followed by amide coupling with 2,6-dimethylaniline. Alternative synthetic routes described in the patent literature include the three-component Ugi-type reaction of formaldehyde, 2,6-dimethylphenyl isocyanide, and 4-aminobutyric acid, followed by cyclization to form the pyrrolidinone ring [5]. The product is purified by recrystallization from water or from ethanol-water mixtures and is characterized by nuclear magnetic resonance spectroscopy, mass spectrometry, and high-performance liquid chromatography. Industrial synthesis yields are typically 75 to 90 percent for the final coupling step. The compound is manufactured as the free base; no salt forms are used in research or clinical preparations.

2. Abstract

Nefiracetam (DM-9384) is a lipophilic pyrrolidinone-type racetam nootropic developed by Daiichi Pharmaceutical (now Daiichi Sankyo) in Japan during the 1980s as a cognition-enhancing agent for cerebrovascular dementia and subsequently investigated for Alzheimer's disease and poststroke affective disorders [3, 6]. The compound is distinguished from the parent racetam piracetam and from other members of the class (aniracetam, oxiracetam, pramiracetam) by its engagement of multiple convergent molecular targets that collectively facilitate hippocampal synaptic transmission and long-term potentiation.

The principal molecular activities, characterized extensively by the Nishizaki laboratory at Kobe University and by the Bhatt and Bhatt groups, are: (a) high-affinity interaction with the GABA-A receptor complex, producing biphasic modulation of GABA-induced currents through a protein kinase A-dependent mechanism [7]; (b) potentiation of neuronal nicotinic acetylcholine receptor (nAChR) currents through a G-protein-coupled protein kinase C pathway, with enhancement at low acetylcholine concentrations and suppression at high concentrations [1, 8]; (c) enhancement of voltage-gated L-type and N-type calcium channel currents through a G-protein-mediated mechanism [2]; (d) potentiation of NMDA receptor function via protein kinase C activation with reduction of the voltage-dependent magnesium block [9]; and (e) facilitation of long-term potentiation in hippocampal CA1 neurons through convergent CaM kinase II and protein kinase C alpha activation [10, 11].

The composite pharmacology produces a long-term-potentiation-like facilitation of hippocampal synaptic transmission that depends principally on presynaptic nicotinic acetylcholine receptor activation and consequent glutamate release [12]. This sustained enhancement of excitatory neurotransmission is the molecular substrate for the cognitive-enhancing activity observed in multiple preclinical models and in clinical populations with dementia.

Clinical development encompassed cerebrovascular dementia (Phase 2 and Phase 3 trials in Japan), Alzheimer's disease (a Phase 2 NINDS-sponsored trial in the United States), and poststroke depression and apathy (randomized controlled trials). In the cerebrovascular dementia program, nefiracetam was at least as effective as idebenone and superior to placebo in large double-blind 8-week trials, with 34.7

percent of patients showing moderate or better general improvement versus 9.8 percent on placebo [6]. The program was halted when a revised Phase 3 trial failed to meet its primary endpoint, and the Japanese New Drug Application was withdrawn in February 2002 [13]. In Alzheimer's disease, the NINDS trial (NCT00001933) showed dose-dependent cognitive improvement at 600 mg and 900 mg daily over 20 weeks, but did not advance beyond Phase 2 [14]. In poststroke apathy, nefiracetam at 900 mg daily produced significant reduction in Apathy Scale scores in a randomized controlled trial [15, 16], though a subsequent confirmatory trial did not replicate the result [17].

The compound is not approved in any jurisdiction. It is available as a research-grade preparation from multiple suppliers at greater than 98 percent purity by HPLC. Investigators should treat the compound as an unapproved research agent and should confirm identity and purity on every lot.

3. Discovery and Development History

3.1 Origin

Nefiracetam was synthesized at Daiichi Pharmaceutical Co., Ltd. (now Daiichi Sankyo Co., Ltd.) in Tokyo, Japan, in the early 1980s as part of a structure-activity program to develop lipophilic piracetam analogs with improved central nervous system penetration and potency for the treatment of cognitive impairment secondary to cerebrovascular disease [3, 6]. The compound was selected from the dimethylphenyl acetamide series on the basis of superior performance in rodent amnesia models (scopolamine-induced, ischemia-induced, and electroconvulsive shock-induced memory deficit paradigms) relative to piracetam and aniracetam at comparable doses. The development code DM-9384 was assigned, and preclinical safety evaluation was initiated in the mid-1980s.

3.2 Japanese clinical development for cerebrovascular dementia

Daiichi advanced nefiracetam through Phase 1 healthy volunteer pharmacokinetic studies in the late 1980s, establishing the dose range, tolerability, and pharmacokinetic profile in Japanese subjects [18]. Phase 2 studies in patients with cognitive impairment secondary to cerebrovascular disease (post-stroke dementia, vascular cognitive impairment) were conducted in the early 1990s, demonstrating cognitive improvement on standardized neuropsychological batteries and tolerability at doses of 300 to 900 mg daily [6]. The compound was at least as effective as idebenone (the then-standard comparator in Japanese cerebrovascular dementia trials) in 8-week double-blind studies. A Phase 3 pivotal trial in patients with sequelae of cerebral infarction was initiated, and the New Drug Application was prepared under the development name Translon.

In a Phase 3 trial, 34.7 percent of 268 patients receiving nefiracetam experienced moderate or better general improvement on a global clinical impression measure, compared to 9.8 percent in the placebo group, a statistically significant difference [6]. However, the regulatory authority requested a revised Phase 3 trial with modified endpoints. The revised trial, conducted through 1999 to 2001, failed to demon-

strate sufficient efficacy on the revised primary endpoint. In February 2002, Daiichi withdrew its New Drug Application in Japan and discontinued the global development program [13]. The compound was never commercially launched as Translon.

3.3 United States development for Alzheimer's disease

Following the characterization of nefiracetam's nicotinic acetylcholine receptor activity by the Nishizaki and Bhatt laboratories [1, 8, 12], the National Institute of Neurological Disorders and Stroke (NINDS) sponsored a Phase 2 randomized, double-blind, placebo-controlled trial of nefiracetam in patients with mild to moderate Alzheimer's disease (ClinicalTrials.gov identifier NCT00001933) [14]. The trial evaluated nefiracetam at 600 mg daily (three 100 mg capsules twice daily) and 900 mg daily (three 150 mg capsules twice daily) versus placebo over 20 weeks. Efficacy was assessed through standardized neuropsychological instruments. Preliminary reports indicated that approximately one-quarter of patients receiving the lower dose and approximately one-half of patients receiving the higher dose showed improved intellectual function. The program was not advanced to Phase 3.

3.4 Poststroke depression and apathy clinical program

Robinson and colleagues at the University of Iowa conducted a series of randomized controlled trials evaluating nefiracetam for poststroke depression and apathy, beginning in the early 2000s [15, 16, 17]. The rationale was based on nefiracetam's cholinergic and monoaminergic facilitation properties and on preclinical evidence of antidepressant-like activity in olfactory bulbectomized rodent models. The clinical results are detailed in Section 7.

3.5 Current status

Nefiracetam is not approved in any jurisdiction as of the current monograph date. The compound is not in active commercial development. It is available as a research-grade preparation from multiple chemical suppliers (Sigma-Aldrich, Cayman Chemical, MedChemExpress, Santa Cruz Biotechnology, TCI Chemicals, BOC Sciences, and others) and is used in preclinical neuroscience research. The compound retains research interest for its unique multi-target pharmacology and for its documented activity at nicotinic acetylcholine receptors, GABA-A receptors, and NMDA receptors, targets that remain central to cognitive pharmacology.

4. Mechanism of Action

Nefiracetam is a multi-target ligand. Its principal molecular activities, characterized in heterologous expression systems, in primary neuronal cultures, and in hippocampal slice preparations, are modulation of GABA-A receptor currents, potentiation of neuronal nicotinic acetylcholine receptor currents, enhancement of voltage-gated calcium channel currents, potentiation of NMDA receptor function, and facilitation of hippocampal long-term potentiation. These activities converge on presynaptic and postsynaptic mechanisms that enhance excitatory neurotransmission in hippocampal and cortical circuits.

4.1 GABA-A receptor modulation

Nefiracetam interacts with the GABA-A receptor chloride channel complex with high affinity. In dorsal root ganglion neurons, nefiracetam produced biphasic modulation of GABA-induced chloride currents: transient potentiation of currents at low GABA concentrations and suppression of currents at high GABA concentrations, with acceleration of current desensitization in both conditions [7]. The binding affinity for [3H]muscimol displacement from GABA-A receptor sites is approximately 8.5 nM (IC₅₀), placing nefiracetam among the highest-affinity racetam-class compounds at this target. The mechanism of the potentiation was characterized as protein kinase A (PKA)-dependent: a PKA inhibitor (KT-5720) blocked the transient potentiation of GABA-activated currents by nefiracetam, and the compound was proposed to inhibit Gi/Go proteins, leading to increased intracellular cyclic AMP levels and PKA system activation [7]. This bidirectional GABA-A modulation distinguishes nefiracetam from classical GABA-A agonists and from benzodiazepine-class positive allosteric modulators and is consistent with a modulatory rather than directly activating mechanism at this receptor.

4.2 Neuronal nicotinic acetylcholine receptor modulation

Nefiracetam modulates neuronal nicotinic acetylcholine receptor (nAChR) currents through a mechanism distinct from direct orthosteric agonism. In rat cortical neurons, nefiracetam augmented currents induced by low concentrations of acetylcholine and suppressed currents induced by high concentrations of acetylcholine

[1, 8]. The modulation was exerted via a pertussis toxin-sensitive G-protein pathway and protein kinase C (PKC): pertussis toxin pretreatment abolished the nefiracetam effect, and PKC inhibitors (chelerythrine, bisindolylmaleimide) blocked the enhancement [8]. The functional consequence of this PKC-dependent nAChR potentiation is a sustained increase in nicotinic receptor sensitivity to endogenous acetylcholine at physiological concentrations, producing a long-lasting facilitation of cholinergic neurotransmission without the rapid desensitization characteristic of direct nicotinic agonists.

The presynaptic nicotinic acetylcholine receptor on hippocampal glutamatergic terminals was identified as a critical functional target. Bhatt and Bhatt (2002) demonstrated that nefiracetam's sustained enhancement of hippocampal synaptic transmission depended on presynaptic nAChR activation and consequent glutamate release [12]. The enhancement was blocked by mecamylamine (a non-selective nAChR antagonist) and by alpha-bungarotoxin (selective for the alpha-7 nAChR subtype), implicating the alpha-7 nicotinic receptor in the mechanism. Bhatt and colleagues further showed that nefiracetam and galantamine (an acetylcholinesterase inhibitor with allosteric nicotinic receptor activity) enhanced excitatory and inhibitory synaptic transmission in rat cortical neurons via stimulation of neuronal nicotinic acetylcholine receptors [19].

4.3 Voltage-gated calcium channel enhancement

Nefiracetam augmented high-voltage-gated N-type and L-type calcium channel currents in cortical neurons at micromolar concentrations (effective concentration range 1 to 100 micromolar) through a G-protein-mediated mechanism distinct from conventional channel activation [2]. The enhancement was characterized by Yoshii and Bhatt (2001) as involving direct G-protein interaction rather than second-messenger cascades, producing a sustained increase in calcium influx during depolarization. The functional consequence is enhanced neurotransmitter release from presynaptic terminals and enhanced calcium-dependent signaling in postsynaptic neurons. The calcium channel enhancement contributes to both the cognitive-enhancing and the neuroprotective activities of the compound.

4.4 NMDA receptor potentiation

Bhatt and colleagues (2007) demonstrated that nefiracetam potentiates NMDA receptor function through protein kinase C activation [9]. Nefiracetam treatment increased PKC alpha activity with a bell-shaped dose-response relationship peaking at 10 nM. The PKC activation produced phosphorylation of NMDA receptor subunits, reduced the voltage-dependent magnesium block of the NMDA channel, and enhanced NMDA-mediated currents. The potentiation was abolished by PKC inhibitors but not by PKA inhibitors, establishing the PKC pathway as the principal mediator. The NMDA receptor potentiation is a key mechanism for the facilitation of long-term potentiation, as NMDA receptor activation is the obligatory induction signal for the Hebbian form of LTP at hippocampal CA1 synapses.

4.5 Facilitation of long-term potentiation

The convergent activation of nicotinic receptors, calcium channels, and NMDA receptors by nefiracetam produces a net facilitation of hippocampal long-term potentiation (LTP). Bhatt and colleagues (1999) demonstrated that nefiracetam induced a long-term-potentiation-like facilitation of hippocampal synaptic transmission that persisted for hours after washout [20]. Moriguchi et al. (2008) characterized the intracellular signaling: nefiracetam enhanced LTP in the rat hippocampal CA1 region through activation of CaM kinase II and protein kinase C, with a bell-shaped dose-response curve [10]. The enhancement required NMDA receptor activation and metabotropic glutamate receptor 5 (mGluR5) stimulation [11]. These findings provide the molecular basis for the cognitive-enhancing activity observed in behavioral models and suggest that the effective concentration range of nefiracetam in the central nervous system coincides with the peak of the bell-shaped dose-response for kinase activation.

4.6 Monoaminergic modulation

Nefiracetam at 1 mg/kg intraperitoneal administration approximately doubled acetylcholine output from the frontal cortex in microdialysis studies in freely moving rats [21]. In addition to the cholinergic effects, nefiracetam has been reported to modulate brain monoamine systems: Hiramatsu et al. (1994) demonstrated effects on serotonergic and dopaminergic turnover in specific brain regions, contributing

to the antidepressant-like behavioral profile [22]. These monoaminergic effects are likely secondary to the primary receptor-level pharmacology rather than direct monoamine receptor binding.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Nefiracetam is rapidly absorbed from the gastrointestinal tract after oral administration. In healthy human volunteers receiving single oral doses of 100 to 600 mg, peak serum concentrations were achieved within 1 to 2 hours [18]. Food intake delayed the time to peak concentration but did not significantly alter the overall area under the concentration-time curve, indicating that food affects the rate but not the extent of absorption. The compound demonstrates linear, dose-proportional pharmacokinetics across the 100 to 900 mg dose range studied in clinical trials [18].

5.2 Distribution

Nefiracetam has moderate tissue distribution consistent with its lipophilic character. The compound crosses the blood-brain barrier readily; its lipophilicity (substantially greater than piracetam owing to the 2,6-dimethylphenyl substituent) supports efficient central nervous system penetration. Specific volume of distribution and plasma protein binding values have not been extensively reported in the published literature; the lipophilicity and rapid onset of central effects in animal models are consistent with a moderate to large apparent volume of distribution.

5.3 Metabolism

Nefiracetam is metabolized predominantly in the liver. The principal metabolic transformation is stereoselective hydroxylation at the 5-position of the pyrrolidine ring, producing 5-hydroxynefiracetam (5-OHN) as the major metabolite, with preferential formation of the (S)-enantiomer [4]. Additional metabolites identified in human urine include the ring-opened product (succinimide derivative) and glucuronide conjugates.

The formation of 5-hydroxynefiracetam is principally mediated by CYP3A4, with a relatively minor contribution from CYP1A2 [23]. The contribution of CYP2C19 and other CYP isoforms is negligible. This metabolic profile suggests susceptibility to

drug-drug interactions with strong CYP3A4 inhibitors and inducers.

Importantly, the metabolite M-18 (a species-specific metabolite formed in dogs and rats but not in humans or primates) is the molecular basis for the nephrotoxicity observed in preclinical toxicology studies in those species [24]. The absence of M-18 formation in human hepatic microsomes and in primate studies provides the pharmacological basis for the absence of renal toxicity in human clinical trials.

5.4 Elimination

Serum concentrations decline monophasically after peak concentration, with elimination half-lives of 3 to 5 hours in healthy volunteers [18]. Less than 10 percent of the administered dose is recovered in urine as unchanged nefiracetam within 24 hours of oral administration, and fecal excretion is less than 0.1 percent of the dose within 24 hours after a 300 mg oral dose [4]. The elimination is therefore predominantly metabolic (hepatic biotransformation) rather than direct renal clearance. Apparent oral clearance values range from 94 to 140 mL/min [18].

5.5 Accumulation and linearity

No clinically significant accumulation of nefiracetam in the body was observed during and after multiple doses in healthy volunteer studies [18]. The compound demonstrates linear pharmacokinetic behavior across the studied dose range, and the absence of accumulation supports twice-daily or three-times-daily dosing regimens without concern for progressive plasma concentration elevation.

5.6 Routes of administration

The principal route of administration in clinical trials and research is oral. Nefiracetam has been administered as capsules (100 mg, 150 mg) in clinical trials at total daily doses of 300 to 900 mg, typically divided into two or three daily administrations [6, 14, 15]. Intraperitoneal administration has been used extensively in pre-clinical studies at doses of 0.01 to 30 mg/kg. Intravenous and subcutaneous routes have been reported in animal pharmacokinetic studies but are not used in clinical applications.

6. Preclinical Pharmacology

6.1 Cognitive enhancement in amnesia models

Nefiracetam has demonstrated antiamnesic activity across a broad range of preclinical models. The compound reversed scopolamine-induced amnesia in passive avoidance and radial maze paradigms in rats at doses of 1 to 10 mg/kg intraperitoneal [3]. In models of amnesia based on GABAergic neuronal dysfunction, nefiracetam at 3 to 10 mg/kg reversed the cognitive deficit [25]. The compound improved spatial learning in rats after experimental cerebral embolism at doses of 1 to 3 mg/kg, with quantitative improvements on the Morris water maze correlating with preservation of hippocampal neuronal density [26].

6.2 Cognitive enhancement in aging models

Deyo and colleagues demonstrated that nefiracetam ameliorated age-related learning deficits in older rabbits using the eyeblink classical conditioning paradigm [27, 28]. The cognitive enhancement was present only when the hippocampus was intact, suggesting that the hippocampus is a critical mediator of the nefiracetam effect and that the compound does not produce generalized central nervous system stimulation. Long-term administration (weeks to months) produced sustained cognitive benefit without tolerance [28].

6.3 Anticonvulsant activity

Nefiracetam possesses anticonvulsant properties in multiple seizure models. Hashimoto et al. (2005) characterized anticonvulsant effects in amygdala-kindled seizures, maximal electroshock, and pentylenetetrazole-induced seizure models in mice and rats [29]. In kainic acid-induced seizures, nefiracetam demonstrated a dissociation between anticonvulsant and neuroprotective activity: the compound dose-dependently inhibited hippocampal neuronal damage without affecting behavioral seizure severity, indicating a neuroprotective mechanism independent of seizure suppression [30]. Nefiracetam also attenuated post-ischemic nonconvulsive seizures in rats and protected against veratridine-induced and glutamate-induced neuronal cell death [31].

6.4 Neuroprotection

The neuroprotective activity of nefiracetam has been demonstrated in multiple paradigms. The compound protected cortical neurons from cell death under serum-free conditions through a mechanism independent of brain-derived neurotrophic factor (BDNF) signaling [32]. The neuroprotective effects are attributed to the convergent calcium channel enhancement (which supports calcium-dependent survival signaling), NMDA receptor modulation (which maintains physiological glutamate signaling while limiting excitotoxicity through the bell-shaped dose-response), and GABAergic modulation (which limits excessive neuronal excitation).

6.5 Antidepressant-like activity

In the olfactory bulbectomized rat model of depression, nefiracetam reversed behavioral deficits and normalized CaM kinase II and protein kinase C activities through NMDA receptor and metabotropic glutamate receptor 5 activation [11]. This preclinical antidepressant-like profile provided the rationale for the clinical investigation of nefiracetam in poststroke depression.

7. Clinical Evidence Base

7.1 Cerebrovascular dementia

The principal clinical application for which nefiracetam was developed is cognitive impairment secondary to cerebrovascular disease. Phase 2 trials conducted in Japan demonstrated cognitive improvement in patients with sequelae of cerebral infarction at doses of 300 to 900 mg daily over 8 to 12 weeks [6]. In the pivotal Phase 3 trial, 34.7 percent of 268 patients receiving nefiracetam experienced moderate or better general improvement on a global clinical impression measure, compared to 9.8 percent in the placebo group [6]. Nefiracetam was at least as effective as idebenone in comparative trials. However, a revised Phase 3 trial conducted from 1999 to 2001, with modified endpoints requested by the Japanese regulatory authority, failed to demonstrate sufficient efficacy on the revised primary endpoint. The New Drug Application was withdrawn in February 2002 [13].

The cognitive improvement observed in the positive trials was characterized as enhanced performance on attention, memory, and executive function measures, consistent with the compound's facilitation of hippocampal and cortical synaptic transmission. The failure of the revised trial has been attributed to endpoint selection, patient heterogeneity within the broad cerebrovascular dementia population, and the inherent difficulty of demonstrating statistically robust cognitive improvement in a population with ongoing vascular injury.

7.2 Alzheimer's disease

The NINDS-sponsored Phase 2 randomized, double-blind, placebo-controlled trial (NCT00001933) evaluated nefiracetam at 600 mg daily and 900 mg daily versus placebo in patients with mild to moderate Alzheimer's disease over 20 weeks [14]. The mechanism of interest was nefiracetam's enhancement of nicotinic acetylcholine receptor activity through the protein kinase C pathway, which differs from the mechanism of currently available cholinesterase inhibitors (donepezil, rivastigmine, galantamine) and was considered potentially complementary. Preliminary reports indicated dose-dependent cognitive improvement: approximately one-quarter of patients receiving 600 mg daily and approximately one-half of patients

receiving 900 mg daily showed improvement on standardized neuropsychological instruments. The compound was well tolerated at both doses. The program did not advance to Phase 3, and detailed efficacy results have not been published in a peer-reviewed journal as of the current monograph date.

7.3 Poststroke depression

Robinson et al. (2008) conducted a double-blind randomized trial of nefiracetam for poststroke depression in 137 stroke patients with major depression, randomized to placebo, 600 mg daily, or 900 mg daily of nefiracetam for at least 4 weeks [15]. The primary endpoint was change in Hamilton Depression Rating Scale scores. The trial did not demonstrate a significant difference between nefiracetam and placebo on the primary depression endpoint at either dose. The compound was well tolerated; adverse events were infrequent and primarily gastrointestinal.

7.4 Poststroke apathy

A secondary analysis of the Robinson 2008 trial identified that 70 of the 137 stroke patients (51.1 percent) also met published diagnostic criteria for apathy [16]. Among these patients, those receiving nefiracetam at 900 mg daily had a significantly greater change in Apathy Scale scores compared to both 600 mg of nefiracetam and placebo. The effect was specific to apathy rather than depression, suggesting a mechanistic dissociation between the compound's effects on motivational versus mood-related circuits.

Starkstein et al. (2016) conducted a confirmatory randomized, placebo-controlled, double-blind trial specifically targeting poststroke apathy [17]. Consenting patients hospitalized with stroke were screened and, if diagnosed with apathy 8 to 36 weeks after stroke, randomized to 12 weeks of 900 mg daily nefiracetam or placebo. The trial did not demonstrate statistically significant differences between nefiracetam and placebo on the Apathy Scale at week 12. The investigators noted that the trial was likely underpowered: 122 patients were expected to participate, but enrollment may have been insufficient to detect the effect size observed in the Robinson secondary analysis.

7.5 Summary of clinical trajectory

The clinical evidence base for nefiracetam spans three indications across approximately 15 years of active investigation. In cerebrovascular dementia, early trials were positive but the pivotal revised Phase 3 trial was negative. In Alzheimer's disease, Phase 2 results were encouraging but the program did not advance. In post-stroke apathy, an initial positive secondary analysis was not confirmed by a dedicated trial. The compound is therefore in a state of clinical evidence that is suggestive of cognitive and motivational benefit at 900 mg daily but that has not produced a registration-quality positive endpoint across any indication.

8. Sourcing and Quality Verification

Research-grade nefiracetam is supplied by multiple chemical and pharmaceutical research suppliers (Sigma-Aldrich, Cayman Chemical, MedChemExpress, Santa Cruz Biotechnology, TCI Chemicals, BOC Sciences, ChemScene, and others) at greater than 98 percent purity by HPLC. Supply is in milligram to gram quantities as the free base. Pricing is moderate, typically in the range of \$30 to \$150 per gram at the time of monograph preparation.

No pharmaceutical-grade marketed product exists, as the compound was never commercially launched in any jurisdiction. The research-grade material from established chemical suppliers is the highest quality available and is the standard source for preclinical and in vitro research.

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 (247.14 for the protonated species $[M+H]^+$; 246.14 for the monoisotopic molecular ion)
- Nuclear magnetic resonance spectroscopy (1H NMR and ^{13}C NMR) confirmation of structural identity, with expected chemical shifts for the 2,6-dimethylphenyl aromatic protons, the pyrrolidinone ring protons, and the acetamide methylene
- Melting point determination (expected 151 to 153 degrees Celsius)
- Residual solvent analysis (gas chromatography of common synthesis solvents)
- Karl Fischer or loss-on-drying analysis for residual water content

Third-party analytical laboratories (Janoshik Analytical, Anabolic Lab, and others) provide independent confirmation of vendor certificates of analysis. Given that nefiracetam was never commercially launched, the research-grade market is the sole supply channel, and on-receipt analytical confirmation is appropriate for any investigation where dose-response or mechanism-of-action precision is important.

9. Reconstitution and Handling

Nefiracetam is supplied as a crystalline powder and is stable at room temperature in dry conditions. For research applications, stock solutions are typically prepared in dimethyl sulfoxide (DMSO) at concentrations of 10 to 100 mM for in vitro work. Aqueous solubility is limited; for preparations requiring aqueous vehicles, the compound can be dissolved in ethanol or DMSO and diluted into aqueous buffer, with the final organic solvent concentration maintained below 0.1 percent for cell-based assays and below 1 percent for tissue-based assays.

Refrigerated storage (2 to 8 degrees Celsius) of the dry powder is recommended for long-term stability; desiccation is appropriate given the compound's limited aqueous solubility. Light protection is not specifically required but is reasonable practice. DMSO stock solutions are stable at negative 20 degrees Celsius for at least 6 months; aqueous dilutions should be prepared fresh for each experiment.

For in vivo preclinical research, the compound is typically dissolved in physiological saline with gentle warming or sonication, or suspended in 0.5 percent methylcellulose for oral gavage administration. Intraperitoneal administration of saline solutions at concentrations of 1 to 10 mg/mL has been the standard in published preclinical studies.

For oral administration in human research, the compound was formulated as capsules (100 mg, 150 mg) in the clinical trials. Investigators preparing research formulations should consider the lipophilic character of the compound and the potential for food-effect delays in absorption when designing dosing schedules.

10. Stack Interactions and Combinations

Nefiracetam interacts with several compound classes through its multi-target pharmacology and its CYP3A4-mediated metabolism. Investigators conducting research with nefiracetam, especially in chronic dosing regimens or in combination with other research compounds, should consider:

CYP3A4 inhibitors: Strong inhibitors (ketoconazole, itraconazole, clarithromycin, ritonavir, grapefruit juice) can substantially elevate nefiracetam exposure by reducing hepatic clearance. Concurrent use should be considered for dose reduction. Moderate inhibitors (erythromycin, diltiazem, verapamil, fluconazole) produce smaller but measurable effects.

CYP3A4 inducers: Strong inducers (rifampin, carbamazepine, phenytoin, phenobarbital, St. John's wort) reduce nefiracetam exposure. Concurrent dosing may compromise efficacy.

Cholinergic agents: Concurrent acetylcholinesterase inhibitors (donepezil, rivastigmine, galantamine) produce additive cholinergic facilitation. The combination is pharmacologically rational for cognitive applications (nefiracetam enhances nicotinic receptor sensitivity while cholinesterase inhibitors increase synaptic acetylcholine), but additive cholinergic adverse events should be expected. Bhatt and colleagues demonstrated complementary mechanisms between nefiracetam and galantamine in vitro [19].

Other racetam-class compounds: Concurrent piracetam, aniracetam, or oxiracetam with nefiracetam has not been systematically studied. The mechanisms overlap at the level of cholinergic facilitation but diverge at the receptor level (nefiracetam's GABA-A and NMDA receptor modulation are not shared by all racetams). Additive cognitive effects are plausible but are not supported by controlled evidence.

GABAergic agents: Nefiracetam's biphasic GABA-A receptor modulation complicates prediction of interactions with benzodiazepines, barbiturates, and other GABA-A-active compounds. The interaction is not straightforward and has not been

characterized in vivo. Caution is appropriate.

NMDA receptor modulators: Concurrent memantine (an uncompetitive NMDA antagonist) and nefiracetam (which potentiates NMDA function) have opposing effects on the NMDA receptor. The net pharmacological result is unpredictable. Concurrent use has not been studied.

Antiepileptic drugs: Nefiracetam's anticonvulsant properties are additive with standard antiepileptic drugs in some seizure models [29]. The clinical significance of this interaction is uncertain, but the combination is pharmacologically rational for seizure management applications.

Choline sources: The nicotinic receptor potentiation by nefiracetam depends on endogenous acetylcholine availability. Concurrent administration of choline sources (alpha-GPC, CDP-choline, phosphatidylcholine) may enhance the nicotinic component of nefiracetam's mechanism by increasing the substrate for acetylcholine synthesis. This combination is commonly reported in research contexts but has not been formally evaluated in controlled studies.

11. Adverse Events and Safety

11.1 Common adverse events in clinical trials

Adverse events reported in clinical trials of nefiracetam are infrequent and primarily gastrointestinal in nature [6, 14, 15]. The principal adverse events at clinical doses (600 to 900 mg daily) include:

- Nausea (mild, transient; reported in less than 10 percent of subjects)
- Gastrointestinal discomfort (reported in less than 5 percent)
- Headache (infrequent)
- Dizziness (infrequent)

Overall tolerability in clinical trials has been comparable to placebo at doses up to 900 mg daily over treatment periods of up to 20 weeks. No clinically significant cardiovascular, hepatic, or renal adverse events have been reported in human subjects.

11.2 Species-specific preclinical toxicology

The principal toxicology concern for nefiracetam is species-specific nephrotoxicity observed in dogs and rats. In a 52-week oral toxicity study in rats, the kidney was identified as the main target organ, with microscopic pathology showing papillary epithelial hyperplasia, collecting duct epithelial hyperplasia, and cortical scarring at doses above 10 mg/kg/day [24]. The no-observed-adverse-effect level in rats was 10 mg/kg/day. Dogs showed heightened sensitivity to renal and testicular toxicity.

The nephrotoxic metabolite M-18 is formed through a metabolic pathway present in dogs and rats but absent in humans and primates [24]. Long-term studies in primates have not demonstrated renal toxicity. The species-specific nature of this toxicity was a significant finding in the development program, as it indicated that the animal toxicology did not predict human risk. Clinical trials in humans at doses of 600 to 900 mg daily (approximately 10 to 15 mg/kg/day in a 60 kg individual) for up to 20 weeks did not produce evidence of nephrotoxicity.

11.3 Reproductive toxicology

Nefiracetam produced testicular toxicity in dogs at high doses, attributed to the same M-18 metabolite pathway. This finding has not been observed in primates or humans. However, investigators should note this species-specific signal when designing long-term preclinical studies in susceptible species.

11.4 Human safety summary

The overall human safety profile of nefiracetam is favorable at doses up to 900 mg daily for treatment periods up to 20 weeks. The absence of the nephrotoxic metabolite M-18 in human metabolism provides mechanistic reassurance regarding the species-specific renal toxicity. No clinically significant safety signals have been identified in the published clinical trial literature. The compound does not appear to produce the cardiovascular, hepatic, or hematological adverse events that limit some other cognitive-enhancing agents.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five racetam-class nootropics against nefiracetam, evaluated against five competency standards: novelty, effect size, promising potential (current research-clinical state and trajectory), side-effect profile (clinical or preclinical), and overall validation. The five comparators were selected as the principal racetam-class compounds with substantive clinical or preclinical evidence in cognitive applications.

12.1 Piracetam

Mechanism: Piracetam is the prototype racetam, acting principally through enhancement of cellular membrane fluidity, facilitation of cholinergic neurotransmission by non-receptor-mediated mechanisms, and modulation of AMPA-type glutamate receptor currents [33, 34]. The compound does not have the high-affinity GABA-A receptor interaction, the PKC-dependent nicotinic receptor potentiation, or the NMDA receptor potentiation that characterize nefiracetam.

Novelty: Low. Piracetam was the first racetam, synthesized in 1964 by UCB Pharma. The mechanism is well established but non-specific relative to newer racetams.

Effect size: Modest. Meta-analyses of piracetam in cognitive impairment have reported small positive effects, with Cochrane reviews concluding insufficient evidence for a clear clinical benefit in dementia [34]. Effect sizes on cognitive measures in individual trials are small (Cohen's *d* typically 0.1 to 0.3).

Promising potential: Low to moderate. Piracetam is approved in numerous European jurisdictions for cognitive impairment and myoclonus but is not approved in the United States. Clinical development for new indications is essentially inactive.

Side-effect profile: Very favorable. Piracetam is well tolerated at doses of 1600 to 4800 mg daily with minimal adverse events. The safety margin is wide.

Overall validation: Moderate. The compound has the longest clinical history of any racetam (over 50 years) and an extensive research literature, but effect sizes are small and clinical utility is debated.

Comparison to nefiracetam: Nefiracetam is substantially more pharmacologically complex than piracetam, engaging GABA-A, nicotinic, calcium channel, and NMDA receptor targets that piracetam does not significantly modulate. Nefiracetam is effective at 10- to 100-fold lower doses in preclinical models. However, piracetam has a much larger clinical safety database and approved indications in multiple jurisdictions. The two compounds share the pyrrolidinone core but diverge significantly in potency, selectivity, and mechanism.

12.2 Aniracetam

Mechanism: Aniracetam is a fat-soluble racetam that acts principally as a positive allosteric modulator of AMPA-type glutamate receptors (ampakine activity), with additional modulation of metabotropic glutamate receptors and cholinergic facilitation [35]. The AMPA receptor potentiation is the distinguishing mechanism and supports both cognitive enhancement and anxiolytic activity.

Novelty: Moderate. The ampakine mechanism was a meaningful advance over piracetam's non-specific activity. Aniracetam was among the first compounds to demonstrate that AMPA receptor positive modulation enhanced cognition.

Effect size: Moderate in preclinical models; limited clinical data. Aniracetam produced robust anti-amnesic effects in scopolamine-induced and ischemia-induced amnesia models at doses of 10 to 100 mg/kg [35]. Clinical trial data in cognitive impairment are limited to small studies in Japan and Europe.

Promising potential: Low. The compound is approved in Japan and some European jurisdictions for cognitive impairment but is not in active clinical development for new indications. Research interest has shifted to newer ampakine compounds.

Side-effect profile: Favorable. Aniracetam is generally well tolerated at doses of 750 to 1500 mg twice daily, with infrequent gastrointestinal and central nervous system adverse events.

Overall validation: Moderate. The compound has a substantive preclinical literature and limited clinical validation. The ampakine mechanism is well supported.

Comparison to nefiracetam: Aniracetam and nefiracetam are both fat-soluble racetams with improved blood-brain barrier penetration relative to piracetam, but they differ mechanistically. Aniracetam's principal target is the AMPA receptor (not significantly engaged by nefiracetam), while nefiracetam's principal targets are the nicotinic receptor, GABA-A receptor, and NMDA receptor (not significantly engaged by aniracetam at clinical concentrations). Both compounds have demonstrated an-tiamnesic activity in overlapping preclinical models. Nefiracetam has a more extensive clinical trial record (multiple Phase 2 and Phase 3 trials) than aniracetam.

12.3 Oxiracetam

Mechanism: Oxiracetam is a water-soluble racetam that enhances choline acetyl-transferase activity in the brain, increasing acetylcholine synthesis, and modulates AMPA-type glutamate receptor currents [36]. The compound is considered a mild cognitive enhancer with effects on attention and logical processing.

Novelty: Low. The mechanism is an incremental modification of the piracetam pharmacology with enhanced cholinergic facilitation.

Effect size: Modest. Oxiracetam has produced positive cognitive effects in small clinical trials in dementia and in post-concussive syndrome, with effect sizes comparable to piracetam [36]. Preclinical effect sizes are moderate in amnesia models.

Promising potential: Low. The compound is approved in some European and Asian jurisdictions for cognitive impairment. It is not in active clinical development for new indications.

Side-effect profile: Favorable. Oxiracetam is well tolerated at doses of 800 to 2400 mg daily.

Overall validation: Moderate. The clinical literature is larger than aniracetam's but smaller than piracetam's.

Comparison to nefiracetam: Oxiracetam shares the cholinergic facilitation mechanism with nefiracetam but lacks the GABA-A receptor modulation, the PKC-dependent nicotinic receptor potentiation, and the NMDA receptor potentiation. Nefiracetam is effective at substantially lower doses (600 to 900 mg daily versus 800 to 2400 mg daily for oxiracetam). Nefiracetam's multi-target pharmacology is more complex than oxiracetam's relatively focused cholinergic and glutamatergic mechanism.

12.4 Pramiracetam

Mechanism: Pramiracetam is a fat-soluble racetam that acts principally through high-affinity uptake of choline into hippocampal neurons, enhancing acetylcholine synthesis and release [37]. The mechanism is more focused on cholinergic facilitation than the other racetams. Pramiracetam is reported to be approximately 30 times more potent than piracetam on a per-milligram basis.

Novelty: Moderate. The high-affinity choline uptake mechanism was a mechanistic advance and supported the development of pramiracetam as a targeted cholinergic enhancer.

Effect size: Moderate. Pramiracetam produced cognitive enhancement in traumatic brain injury patients in a small placebo-controlled trial and reversed scopolamine-induced amnesia in healthy volunteers [37]. Effect sizes are moderate.

Promising potential: Low to moderate. The compound is approved in some European jurisdictions for cognitive impairment. It is not in active clinical development for new indications.

Side-effect profile: Favorable. Pramiracetam is well tolerated at doses of 300 to 600 mg twice daily. Headache is the most commonly reported adverse event, potentially attributable to cholinergic facilitation exceeding choline availability.

Overall validation: Low to moderate. The clinical literature is limited, with small sample sizes in published trials.

Comparison to nefiracetam: Pramiracetam and nefiracetam both enhance cholinergic neurotransmission but through different mechanisms: pramiracetam through choline uptake facilitation, nefiracetam through PKC-dependent nicotinic receptor potentiation. Nefiracetam's additional GABA-A, calcium channel, and NMDA receptor modulation provides a broader mechanistic profile. Both compounds are fat-soluble and brain-penetrant. Nefiracetam has a more extensive clinical trial record.

12.5 Levetiracetam

Mechanism: Levetiracetam is a racetam derivative developed and approved primarily as an antiepileptic drug rather than a nootropic [38]. The principal mechanism is binding to synaptic vesicle glycoprotein 2A (SV2A), which modulates neuro-

transmitter release. Unlike the nootropic racetams, levetiracetam's primary therapeutic application is seizure control rather than cognitive enhancement.

Novelty: High within the racetam class. The SV2A mechanism is unique among racetams and supports a distinct therapeutic profile.

Effect size: High for seizure control (the approved indication). Cognitive effects are mixed; some patients report cognitive side effects (somnolence, psychomotor slowing) while others show cognitive preservation in the context of seizure control.

Promising potential: High for the approved antiepileptic indication. Low for cognitive enhancement per se.

Side-effect profile: Moderate. Somnolence, behavioral changes (irritability, aggression), and dizziness are reported at therapeutic antiepileptic doses [38]. The side-effect profile is less favorable than the nootropic racetams for cognitive applications.

Overall validation: High for the antiepileptic indication. Low for cognitive enhancement.

Comparison to nefiracetam: Levetiracetam and nefiracetam share the pyrrolidine core structure and both possess anticonvulsant properties, but they diverge sharply in mechanism (SV2A versus multi-target modulation) and therapeutic profile (antiepileptic versus nootropic). Nefiracetam's anticonvulsant properties are secondary to its cognitive-enhancing profile, while levetiracetam's cognitive effects are secondary to its antiepileptic profile. The comparison illustrates the mechanistic diversity achievable within the racetam structural class.

12.6 Comparator summary

The five racetam-class comparators occupy distinct pharmacological positions. **Piracetam** is the prototype with the longest history but lowest potency and smallest effect sizes. **Aniracetam** introduces ampakine (AMPA receptor) activity and lipophilicity but lacks nefiracetam's nicotinic and GABA-A receptor engagement. **Oxiracetam** provides focused cholinergic and glutamatergic facilitation at moderate potency. **Pramiracetam** is a potent cholinergic enhancer through choline uptake facilitation. **Levetiracetam** represents a mechanistic outlier with SV2A-mediated antiepileptic activity.

Nefiracetam occupies a unique position in this comparator landscape: it is the most pharmacologically complex of the nootropic racetams, engaging GABA-A receptors, neuronal nicotinic receptors, voltage-gated calcium channels, and NMDA receptors through convergent protein kinase pathways. It is the only racetam with documented high-affinity GABA-A receptor interaction (IC₅₀ approximately 8.5 nM). It has the most extensive clinical trial record among the non-approved nootropic racetams, with multiple Phase 2 and Phase 3 trials across three indications. Its principal limitation is the absence of a positive registration-quality Phase 3 endpoint, a limitation shared by aniracetam and pramiracetam in their non-approved indications.

The multi-target pharmacology of nefiracetam, while a potential strength for addressing the multifactorial pathology of cognitive impairment, may also have contributed to the difficulty in demonstrating clear efficacy on single primary endpoints in registration trials. The bell-shaped dose-response relationship observed for protein kinase C activation and for LTP enhancement adds further complexity to dose optimization in clinical settings. Investigators considering nefiracetam for cognitive research should appreciate both the mechanistic richness and the dose-response complexity of the compound relative to the more pharmacologically focused comparators.

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