

RESEARCH MONOGRAPH . COMPOUND PROFILE

Hemantane

An aminoadamantane-class antiparkinsonian agent developed at the Zakusov Institute of Pharmacology in Russia, distinguished from amantadine and memantine by a hexamethylenimine substituent that confers a broader pharmacological spectrum encompassing NMDA receptor channel blockade, selective monoamine oxidase B inhibition, dopamine transporter modulation, and anti-inflammatory activity.

DOCUMENT	KDC-MN-1579
ISSUED	2026-05-20
REVISION	1.0
AUTHOR	Kodi ^{ac} bio ^l abs Research
COMPOUND CLASS	Aminoadamantane derivative with low-affinity noncompetitive NMDA receptor antagonism, selective MAO-B inhibition, and dopaminergic modulation

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ABSTRACT

Hemantane (N-(2-adamantyl)hexamethyleneimine hydrochloride; gimantan) is an experimental antiparkinsonian and neuroprotective agent of the aminoadamantane structural class, synthesized and developed at the V.V. Zakusov Research Institute of Pharmacology of the Russian Academy of Medical Sciences. The compound shares the adamantane cage scaffold with the clinically established agents amantadine and memantine but is distinguished by the attachment of a seven-membered azepane (hexamethylenimine) ring at the 2-position of the adamantane nucleus, a modification that broadens the pharmacological profile relative to the parent aminoadamantanes. Hemantane acts through multiple convergent mechanisms: it is a low-affinity, noncompetitive (uncompetitive) open-channel blocker of the N-methyl-D-aspartate (NMDA) subtype of the ionotropic glutamate receptor; a weak, competitive, selective inhibitor of monoamine oxidase B (MAO-B; K_i approximately 470 micromolar); a noncompetitive modulator of the dopamine transporter (DAT) that acutely reduces striatal dopamine reuptake V_{max} by approximately 30 percent; a modulator of dopamine receptor subtype density (upregulating D1 and downregulating D2/D3 binding sites in the striatum after subchronic administration); and a putative sigma receptor agonist. The compound also exhibits anti-inflammatory activity in models of peripheral inflammation (acetic acid peritonitis, carrageenan-induced paw edema) and in a lipopolysaccharide-induced neuroinflammation model of Parkinson disease, where it attenuated weight loss, contralateral forepaw akinesia, and olfactory behavioral disruption.

In preclinical parkinsonism models, hemantane (10 to 20 mg/kg intraperitoneally) reduced tremor, rigidity, and oligokinesia, and was reported to be superior to the reference drug amantadine in several behavioral paradigms. In the MPTP-treated C57BL/6 mouse model, subchronic hemantane administration increased dopamine transporter levels in multiple brain structures, a response broader than that produced by amantadine. A single administration of hemantane (20 mg/kg) in C57BL/6 mice reduced striatal DOPA concentration, decreased serotonin and its metabolite levels in the striatum, and altered the homovanillic acid to dopamine ratio in the frontal cortex, demonstrating modulatory activity across both dopaminergic and serotonergic systems.

Clinical evaluation of hemantane has been conducted in a randomized, double-blind, placebo-controlled Phase 2 trial in 60 patients with newly diagnosed, untreated early-stage Parkinson disease over 16 weeks. Hemantane at 50 mg daily (25 mg twice daily) produced a 41 percent reduction in rigidity from baseline and statistically significant improvement on the Unified Parkinson's Disease Rating Scale (UPDRS) Part III motor examination scores at weeks 8, 12, and 16 compared with placebo. The 25 mg daily dose produced moderate efficacy. Safety monitoring (blood pressure, electrocardiogram, blood and urine parameters) did not identify dose-limiting toxicity at either dose. Additional preclinical research has demonstrated analgesic activity in somatic and visceral pain models, efficacy in reducing ethanol consumption in alcohol-experienced rats, attenuation of morphine withdrawal signs, and anti-arthritic activity when applied as a 5 percent topical gel formulation. The compound has not received marketing authorization in any jurisdiction and remains an investigational agent. This monograph documents the chemistry, synthesis, multi-target pharmacology, preclinical and

clinical evidence, sourcing considerations, and a comparative assessment of hemantane against five structurally or mechanistically related compounds on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Hemantane (not formally assigned by WHO; hemantane is the conventional transliteration used in the English-language pharmacological literature).

Alternative transliterations and trade names: Hymantane, Gimantane, Gimantan. The Russian-language pharmaceutical literature uses the Cyrillic form. Gimantan is the name under which a 50 mg tablet formulation has been standardized [1].

Development designation: The compound was developed at the V.V. Zakusov Research Institute of Pharmacology (formerly the Institute of Pharmacology, Russian Academy of Medical Sciences) under the laboratory designation that produced the first publications in approximately 1999 to 2000 [2].

Chemical Abstracts Service registry number: 299424-44-5.

PubChem Compound Identifier (CID): 9838302.

ChemSpider Identifier: 8014022.

International Union of Pure and Applied Chemistry name: 1-(adamantan-2-yl)azepane. The compound is the N-alkylated product of azepane (hexamethylenimine, the seven-membered saturated nitrogen heterocycle) at the 2-position of the adamantane cage.

1.2 Structural class and chemistry

Hemantane belongs to the aminoadamantane structural class, a family of polycyclic cage amine derivatives that includes the clinically established agents amantadine (1-aminoadamantane), memantine (1-amino-3,5-dimethyladamantane), and rimantadine (1-(1-adamantyl)ethylamine). The distinguishing structural feature of hemantane relative to these agents is the replacement of the primary amine or simple secondary amine substituent with a seven-membered azepane ring attached at the 2-position (rather than the 1-position) of the adamantane cage. This substitution

pattern alters the steric and electronic environment of the nitrogen atom and modifies the lipophilicity, conformational flexibility, and receptor interaction profile relative to the 1-amino-substituted parent compounds [3].

Molecular formula: C₁₆H₂₇N (free base); C₁₆H₂₈ClN (hydrochloride salt).

Molecular weight: 233.40 g/mol (free base); 269.86 g/mol (hydrochloride salt).

SMILES notation: C1CCCN(CC1)C2C3CC4CC(C3)CC2C4.

InChI Key: JAROVUWOMYMQCW-UHFFFAOYSA-N.

Physical properties: The hydrochloride salt is a white to off-white crystalline powder. The free base is a moderately lipophilic amine. The adamantane cage confers metabolic stability and blood-brain barrier penetration characteristic of the aminoadamantane class. Solubility of the hydrochloride salt in water is sufficient for oral and parenteral formulation. The compound is supplied as a 50 mg tablet for clinical investigation [1].

1.3 Synthesis

Hemantane is synthesized via a modified Leuckart reaction, a classical reductive amination procedure applied to carbonyl compounds and amines in the presence of formic acid [4]. The synthesis involves heating adamantanone (2-adamantanone) with azepane (hexamethylenimine) in the presence of formic acid, producing the N-formyl intermediate, which is subsequently hydrolyzed to yield the free base amine. The hydrochloride salt is prepared by treatment with hydrogen chloride in an appropriate solvent.

The Leuckart reaction is well established for the synthesis of N-alkylated amines from ketones and is particularly suited to the adamantane system because the cage ketone is resistant to enolization and side reactions. The use of 2-adamantanone (rather than 1-adamantanone, which does not exist as a stable species) directs substitution to the 2-position of the cage, producing the characteristic 2-amino substitution pattern that distinguishes hemantane from the 1-amino-substituted amantadine and memantine [4, 5].

Industrial preparation follows this general route with optimization for yield, purity, and salt formation. Characterization is by nuclear magnetic resonance spectroscopy, mass spectrometry, and high-performance liquid chromatography. The

compound does not possess a conventional stereocenter in the classical sense; the 2-position of the adamantane cage can adopt two orientations (axial and equatorial substitution), but the conformational dynamics of the cage system and the nitrogen substituent produce a single stable geometric isomer under standard conditions.

2. Abstract

Hemantane (N-(2-adamantyl)hexamethyleneimine hydrochloride) is a multi-target aminoadamantane derivative developed at the Zakusov Institute of Pharmacology as an antiparkinsonian and neuroprotective agent. The compound was first described in the Russian pharmacological literature in approximately 1999 to 2000 and has been the subject of an expanding preclinical and early clinical research program over the subsequent two decades [2, 6].

The pharmacological profile of hemantane is defined by at least five characterized molecular activities: (1) low-affinity, noncompetitive (uncompetitive) open-channel blockade of the NMDA subtype of the ionotropic glutamate receptor, a mechanism shared with amantadine and memantine and associated with neuroprotection against excitotoxic neuronal injury; (2) selective, weak, competitive inhibition of monoamine oxidase B (MAO-B), the mitochondrial enzyme responsible for oxidative deamination of dopamine and phenylethylamine in the central nervous system; (3) noncompetitive modulation of the dopamine transporter (DAT), producing acute suppression of striatal dopamine reuptake and thereby increasing synaptic dopamine availability; (4) modulation of dopamine receptor subtype expression, with upregulation of D1 receptor density and downregulation of D2 and D3 receptor density in the striatum after subchronic administration; and (5) putative sigma receptor agonism, a property shared with other aminoadamantane derivatives and hypothesized to contribute to dopaminergic facilitation [7, 8, 9, 10].

In preclinical models of parkinsonism, hemantane at doses of 10 to 20 mg/kg intraperitoneally reduced the cardinal motor features of tremor, rigidity, and oligokinesia and was reported to be superior to equimolar doses of amantadine in several behavioral paradigms. The compound demonstrated neuroprotective activity in the MPTP-treated C57BL/6 mouse model, increasing dopamine transporter expression in multiple brain regions after subchronic administration [11]. In the lipopolysaccharide-induced neuroinflammation model, hemantane attenuated weight loss, contralateral forepaw akinesia, and olfactory behavioral disruption, consistent with both neuroprotective and anti-inflammatory activity [12].

Clinical evaluation has been limited to a single randomized, double-blind, placebo-controlled Phase 2 trial in 60 patients with newly diagnosed, untreated Parkinson disease. Hemantane at 50 mg daily (25 mg twice daily) for 16 weeks produced a 41 percent reduction in rigidity from baseline and significant improvement on UPDRS Part III motor examination scores compared with placebo [13]. Safety monitoring did not identify dose-limiting toxicity. The compound has not received marketing authorization in any jurisdiction.

Additional preclinical research has extended the pharmacological characterization of hemantane to analgesic, anti-addictive, and anti-inflammatory domains, positioning the compound as a candidate for investigation across multiple central nervous system and peripheral inflammatory conditions.

3. Discovery and Development History

3.1 Origin

Hemantane was synthesized at the V.V. Zakusov Research Institute of Pharmacology (formerly the Institute of Pharmacology of the Russian Academy of Medical Sciences) in Moscow as part of a systematic exploration of aminoadamantane derivatives for antiparkinsonian activity. The medicinal chemistry rationale was to modify the aminoadamantane scaffold of amantadine (which had been in clinical use for Parkinson disease since the late 1960s) by varying the nitrogen substituent and the position of attachment to the adamantane cage, with the goal of identifying derivatives with broader or more potent pharmacological activity [2, 6].

The selection of azepane (hexamethylenimine) as the nitrogen substituent and the 2-position of the adamantane cage as the attachment point produced a compound with enhanced lipophilicity and altered receptor pharmacology relative to amantadine. Early screening in animal models of parkinsonism (haloperidol-induced catalepsy, reserpine-induced akinesia, and MPTP-induced parkinsonism) demonstrated that hemantane reduced parkinsonian motor features at doses that were active in the same models where amantadine required higher doses or produced less complete responses [2].

3.2 Preclinical characterization

The preclinical pharmacology of hemantane was characterized in a series of studies conducted primarily at the Zakusov Institute from approximately 2000 to 2015. The characterization proceeded in stages: initial demonstration of antiparkinsonian activity in behavioral models; identification of the NMDA receptor channel-blocking mechanism by electrophysiology and binding studies; characterization of MAO-B inhibition; investigation of dopamine transporter modulation; characterization of dopamine receptor subtype changes; and investigation of anti-inflammatory and neuroprotective activity in neuroinflammation models [7, 8, 9, 10, 11, 12].

The breadth of the preclinical pharmacology, spanning at least five receptor or transporter targets, is unusual for an aminoadamantane derivative and distinguishes hemantane from both amantadine (for which NMDA antagonism and

dopamine release are the principal characterized mechanisms) and memantine (for which NMDA antagonism with voltage-dependent kinetics is the principal mechanism and the basis of clinical approval for Alzheimer disease).

3.3 Clinical development

Hemantane entered clinical evaluation in a Phase 2 study conducted in Russia in patients with early Parkinson disease. The study, reported as an abstract at the International College of Neuropsychopharmacology (CINP) World Congress in 2016, enrolled 60 patients with newly diagnosed, untreated Parkinson disease in a randomized, double-blind, placebo-controlled design across three arms (25 mg daily, 25 mg escalated to 50 mg daily, and placebo) for 16 weeks [13]. The 50 mg dose produced significant motor improvement. No full-length peer-reviewed publication of this trial has appeared in the English-language literature as of the monograph revision date.

The compound has not advanced to Phase 3 registration trials and has not received marketing authorization in Russia or in any other jurisdiction. The 50 mg tablet formulation has been standardized but is not commercially available. The current status of hemantane is that of an investigational compound with a substantial preclinical evidence base and limited early-phase clinical data.

4. Mechanism of Action

Hemantane is a multi-target ligand. Its principal molecular activities, characterized in binding assays, electrophysiological studies, enzyme kinetics, and behavioral pharmacology, are (1) NMDA receptor channel blockade, (2) MAO-B inhibition, (3) dopamine transporter modulation, (4) dopamine receptor subtype modulation, and (5) putative sigma receptor agonism. These activities operate at overlapping concentration ranges and contribute differentially to the observed antiparkinsonian, neuroprotective, analgesic, and anti-inflammatory effects.

4.1 NMDA receptor antagonism

The N-methyl-D-aspartate (NMDA) receptor is a heteromeric ligand-gated cation channel of the ionotropic glutamate receptor superfamily, composed principally of GluN1 and GluN2 subunits. It is expressed throughout the central nervous system and plays a central role in synaptic plasticity, excitotoxicity, and neurodegenerative pathophysiology. Excessive NMDA receptor activation by glutamate contributes to excitotoxic neuronal death in Parkinson disease, Alzheimer disease, stroke, and other neurodegenerative conditions.

Hemantane blocks the NMDA receptor ion channel in a low-affinity, noncompetitive (uncompetitive), voltage-dependent manner, binding within the open channel pore and preventing cation flux [6, 14]. This mechanism is shared with amantadine and memantine, both of which are clinically established NMDA receptor channel blockers. The low-affinity, open-channel blocking kinetics are therapeutically significant: they permit the compound to block excessive (pathological) NMDA receptor activation while sparing the normal (physiological) synaptic signaling that is essential for learning and memory. This kinetic selectivity distinguishes the aminoadamantane channel blockers from high-affinity NMDA antagonists (phencyclidine, dizocilpine/MK-801) that produce psychotomimetic effects and are not clinically viable.

Hemantane has been shown to reduce calcium and sodium fluxes through NMDA channels in cultured rat brain neurons, producing neuroprotective effects against NMDA-mediated excitotoxicity [14]. The neuroprotective profile is consis-

tent with the broader aminoadamantane class and is the mechanistic basis for the anti-excitotoxic and anti-inflammatory downstream effects.

4.2 Monoamine oxidase B inhibition

Monoamine oxidase B (MAO-B) is a mitochondrial flavoenzyme that catalyzes the oxidative deamination of dopamine, phenylethylamine, and benzylamine. MAO-B activity increases with age and is elevated in the parkinsonian brain; its inhibition increases synaptic dopamine availability and reduces the generation of hydrogen peroxide and aldehyde metabolites that contribute to oxidative neuronal damage. Selective, irreversible MAO-B inhibitors (selegiline, rasagiline, safinamide) are established therapies for Parkinson disease.

Hemantane acts as a weak, competitive, selective inhibitor of MAO-B with a K_i of approximately 470 micromolar [7]. The compound does not significantly inhibit MAO-A at the same concentrations. Although the MAO-B inhibitory potency is substantially lower than that of the irreversible inhibitors selegiline and rasagiline, the reversible and competitive nature of the inhibition may contribute to the overall dopaminergic facilitation observed in vivo, particularly in combination with the NMDA receptor blockade and dopamine transporter modulation. An interaction between hemantane and selegiline has been characterized: in vitro, hemantane partially protected MAO-B from irreversible inactivation by selegiline, while in vivo the combination enhanced selegiline-mediated MAO-B inhibition [7].

4.3 Dopamine transporter modulation

The dopamine transporter (DAT) is the principal mechanism for synaptic dopamine clearance in the striatum and other dopaminergic terminal fields. Modulation of DAT function directly affects synaptic dopamine concentration and is relevant to the therapeutic mechanism of agents used in Parkinson disease.

Hemantane modulates DAT function through a noncompetitive mechanism. Acute administration of hemantane (40 mg/kg intraperitoneally in rats) produced a 30 percent decrease in the apparent V_{max} of [3H]-dopamine reuptake in striatal synaptosomes without changing the apparent K_m , indicating noncompetitive suppression of transporter function rather than direct competition at the substrate-

binding site [8]. Subchronic administration (20 mg/kg daily for 7 days) produced a contrasting 17 percent increase in apparent Vmax, suggesting neuroadaptive upregulation of transporter capacity with repeated dosing [8].

In the MPTP-treated C57BL/6 mouse model, subchronic hemantane administration increased DAT levels in multiple brain structures (striatum and frontal cortex), a response that was broader in regional scope than that produced by amantadine, which increased DAT levels only in the striatum [11]. The functional implication is that hemantane produces both an acute dopamine-enhancing effect (through transporter suppression) and a chronic trophic effect (through transporter upregulation), a biphasic profile that may be advantageous for sustained dopaminergic support in Parkinson disease.

4.4 Dopamine receptor subtype modulation

Subchronic administration of hemantane (20 mg/kg daily for 7 days, intraperitoneally in rats) produced measurable changes in dopamine receptor subtype density in the striatum: increased density of D1 receptor binding sites and decreased density of D2 and D3 receptor binding sites, without changes in binding affinity to selective radioligands [9]. The D1 receptor upregulation is directionally consistent with enhanced direct-pathway striatal output (which facilitates movement), while the D2/D3 receptor downregulation may reflect a compensatory response to increased synaptic dopamine availability produced by the DAT modulation.

The receptor subtype modulation profile is distinct from that of amantadine and from that of direct dopamine receptor agonists (pramipexole, ropinirole), and may contribute to the qualitative differences in motor response observed between hemantane and amantadine in preclinical comparisons.

4.5 Sigma receptor agonism

Hemantane has been theorized to act as a sigma receptor agonist, a property shared with amantadine and memantine [3]. Sigma receptors (sigma-1 and sigma-2) are intracellular chaperone proteins expressed in endoplasmic reticulum membranes; sigma-1 receptor activation modulates calcium signaling, dopamine release, and neuroprotection. The sigma receptor agonism has not been directly quantified for

hemantane (no binding affinity or functional potency values have been published), but it is hypothesized to contribute to the dopaminergic facilitation and neuroprotective effects observed in vivo.

4.6 Anti-inflammatory mechanisms

Hemantane exhibits anti-inflammatory activity through mechanisms that are at least partially independent of the NMDA receptor blockade. In models of peripheral inflammation (acetic acid peritonitis, carrageenan-induced paw edema, concanavalin A-induced paw edema), hemantane at 10 to 40 mg/kg intraperitoneally reduced inflammatory exudate and edema with efficacy comparable to diclofenac sodium, but without the ulcerogenic activity that characterizes nonselective cyclooxygenase inhibitors [12, 15]. The proposed anti-inflammatory mechanism involves modulation of calcium-dependent inflammatory cascades downstream of NMDA receptor activation, including regulation of cyclooxygenase-2 (COX-2) expression (which is transsynaptically regulated via NMDA receptors in neurons) and inhibition of phospholipase A2 activity [12, 15].

In the lipopolysaccharide (LPS)-induced neuroinflammation model, hemantane at 10 mg/kg daily attenuated the microglial activation, weight loss, motor impairment, and olfactory behavioral disruption produced by unilateral LPS injection into the substantia nigra, consistent with central anti-inflammatory and neuroprotective activity [12]. The NMDA receptor blockade on T-cells, which express functional NMDA receptors that modulate proliferation and migration, has been proposed as an additional immunomodulatory mechanism relevant to the anti-arthritic activity observed with topical hemantane formulations [15].

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Detailed human pharmacokinetic parameters for hemantane have not been published in the English-language literature. The clinical trial used oral administration of 25 mg and 50 mg tablet formulations, indicating that the compound is orally bioavailable at these doses [13]. The aminoadamantane structural class is generally characterized by good oral bioavailability (amantadine approximately 86 to 94 percent, memantine approximately 100 percent), and the moderate lipophilicity of the hemantane molecule (conferred by the adamantane cage and the azepane ring) is consistent with favorable gastrointestinal absorption.

5.2 Distribution

The adamantane cage structure confers blood-brain barrier penetration characteristic of the aminoadamantane class. Amantadine and memantine achieve brain concentrations that are approximately 1.5 to 10-fold higher than plasma concentrations; hemantane is expected to exhibit similar central nervous system penetration based on structural analogy and the demonstrated central pharmacological effects (dopamine transporter modulation in striatum and frontal cortex, biogenic monoamine changes in striatum, frontal cortex, and hippocampus, and bioelectric activity changes in the MPTP model) [10, 11, 16]. Specific volume of distribution, plasma protein binding, and tissue distribution data have not been published.

5.3 Metabolism

Metabolic pathways for hemantane have not been characterized in published studies. By structural analogy with other aminoadamantane derivatives, hepatic oxidative metabolism (hydroxylation of the adamantane cage, oxidation of the azepane ring) mediated by cytochrome P450 enzymes is expected. Amantadine is primarily excreted unchanged by the kidney, while memantine undergoes partial hepatic hy-

droxylation and glucuronidation. The larger and more lipophilic azepane substituent of hemantane may shift the metabolic balance toward greater hepatic oxidation relative to amantadine.

5.4 Elimination

Elimination parameters (plasma half-life, renal clearance, hepatic extraction ratio) have not been published for hemantane. The dosing regimen in the clinical trial (25 mg once daily or 25 mg twice daily) suggests a half-life in the range of 8 to 24 hours, consistent with once- or twice-daily oral dosing [13]. For reference, amantadine has a plasma half-life of approximately 10 to 31 hours and memantine approximately 60 to 80 hours; the hemantane half-life is expected to fall within or near this range based on structural considerations.

5.5 Preclinical pharmacokinetic context

Preclinical studies used intraperitoneal administration at doses of 10 to 40 mg/kg in mice and rats, with pharmacodynamic effects (dopamine reuptake changes, monoamine level changes, behavioral responses) measured at 1 hour to several hours post-injection [8, 10]. The acute toxicity (LD50) at 0.2 LD50 corresponds to approximately 114 mg/kg in rats when administered orally, indicating a substantial therapeutic index relative to the preclinical efficacy dose range of 10 to 20 mg/kg [12].

5.6 Routes of administration

Two routes have been used in hemantane research: oral (25 to 50 mg daily in human clinical trials; standardized as a 50 mg tablet formulation) and intraperitoneal (10 to 40 mg/kg in rodent preclinical studies). A topical formulation (5 percent hemantane gel) has been developed and tested in the Freund's complete adjuvant-induced arthritis model in rats, with local application to affected joints producing measurable anti-inflammatory and analgesic effects [15]. Intravenous and subcutaneous routes have not been reported.

6. Preclinical Pharmacology

6.1 Antiparkinsonian activity

Hemantane has been evaluated in multiple preclinical models of parkinsonism. In the MPTP-treated C57BL/6 mouse model, which produces selective dopaminergic neuron degeneration in the substantia nigra and is the standard rodent neurotoxic model of Parkinson disease, hemantane demonstrated neuroprotective activity as measured by dopamine transporter expression, behavioral endpoints, and bioelectric activity [11, 16].

In haloperidol-induced catalepsy and reserpine-induced akinesia models, hemantane at 10 to 20 mg/kg intraperitoneally reduced parkinsonian motor features and was reported to be superior to amantadine at equimolar or equivalent doses in several measures [2, 6]. The superiority to amantadine in these paradigms provided the preclinical rationale for advancing hemantane to clinical evaluation.

A comparative study of hemantane and amantadine effects on dopamine transporter expression in normal and MPTP-treated C57BL/6 mice demonstrated that subchronic hemantane (7 daily injections of 20 mg/kg) increased DAT levels in both striatum and frontal cortex, while amantadine (7 daily injections of 13.9 mg/kg, an equimolar dose) increased DAT only in the striatum [11]. This broader regional effect of hemantane on dopaminergic terminal marker expression suggests a more comprehensive trophic or compensatory response to the drug.

6.2 Neuroprotection in neuroinflammation models

The LPS-induced neuroinflammation model replicates key features of the inflammatory component of Parkinson disease pathogenesis: microglial activation, release of proinflammatory cytokines (tumor necrosis factor-alpha, interleukin-1-beta, interleukin-6), and progressive dopaminergic neuronal degeneration. Hemantane at 10 mg/kg daily (initiated one day before stereotaxic LPS injection into the left substantia nigra pars compacta) produced the following effects [12]:

Weight loss: The LPS control group lost 12.2 g by day 3 and an additional 11.9 g by day 8 post-injection. Hemantane-treated animals showed weight loss reduced by a factor of 1.3 on day 3 and by a factor of 3.5 on day 8.

Motor function (cylinder test): Right forelimb use dropped by 17.7 percent compared with sham-operated animals in the LPS group. Hemantane produced a twofold decrease in the loss of contralateral paw activity relative to the LPS group.

Olfactory function: At 3 weeks post-injection, hemantane-treated animals spent significantly more time in the zone of minimal odorant exposure and made significantly fewer crossings into the zone of maximal irritating citrus odor, indicating preservation of olfactory discrimination.

6.3 Effects on biogenic monoamines

A single administration of hemantane (20 mg/kg intraperitoneally) in C57BL/6 mice produced measurable changes in monoamine neurotransmitter levels across multiple brain structures [10]: decreased DOPA concentration in the striatum (consistent with gentle inhibition of dopamine synthesis or increased dopamine turnover); reduced serotonin levels and serotonin metabolite concentrations in the striatum; and alteration of the homovanillic acid to dopamine ratio in the frontal cortex. These neurochemical effects demonstrate that hemantane modulates both dopaminergic and serotonergic transmission and that the effects are not confined to a single brain region.

6.4 Analgesic activity

Hemantane exhibits analgesic activity in multiple pain models. At 20 mg/kg intraperitoneally, the compound demonstrated analgesia in the somatic thermal pain model (tail-flick test) and the visceral pain model (acetic acid-induced writhing test) in mice [17]. In the hot-plate test, hemantane at 10 and 20 mg/kg increased pain thresholds dose-dependently at 180 and 240 minutes after administration, indicating a delayed-onset, sustained analgesic effect [17, 18].

The analgesic mechanism involves both NMDA receptor antagonism (which reduces central sensitization and wind-up phenomena in dorsal horn nociceptive processing) and a dopaminergic component, as demonstrated by the attenuation of

hemantane analgesia by dopamine receptor antagonists [17]. This dual analgesic mechanism distinguishes hemantane from pure NMDA antagonists and from pure dopaminergic agents.

In a topical formulation (5 percent gel), hemantane reduced hind paw edema, hyperalgesia, and motor deficits in the Freund's complete adjuvant-induced arthritis model in rats, with effects comparable to 1 percent diclofenac gel [15]. Hemantane increased hind paw withdrawal latency by 23.0 percent (left) and 34.0 percent (right) in thermal pain testing and improved rotarod performance by 74.3 percent versus diseased controls. Histological examination showed that hemantane reduced degenerative-dystrophic lesions of cartilage tissue more effectively than diclofenac gel. Notably, hemantane caused no mortality in the arthritis model, while diclofenac caused four deaths among ten treated rats [15].

6.5 Anti-addictive activity

Hemantane has been evaluated in preclinical models of substance use disorders. In the ethanol self-administration paradigm, hemantane at 20 mg/kg daily for 14 days (intraperitoneally) significantly reduced daily ethanol intake in random-bred male rats with established alcohol preference under free-choice conditions [19]. The anti-alcohol effect is consistent with the NMDA receptor antagonist mechanism, as glutamatergic neurotransmission is critically involved in the reinforcing and motivational properties of ethanol, and NMDA receptor antagonists have been shown to reduce ethanol consumption in multiple preclinical paradigms.

In the morphine withdrawal model, a single intraperitoneal injection of hemantane at 10 or 20 mg/kg significantly and dose-dependently moderated behavioral withdrawal symptoms (teeth-chattering, ptosis, vocalization) and reduced the total withdrawal score [20]. Under the same conditions, amantadine at 10 or 20 mg/kg decreased motor activity and promoted body weight loss but did not significantly reduce the total withdrawal score, demonstrating an advantage of hemantane over the reference aminoadamantane in this paradigm [20].

6.6 DNA integrity and genotoxicity

A study using the DNA comet assay (single-cell gel electrophoresis) evaluated the effects of MPTP and hemantane on DNA integrity in the striatum and frontal cortex of C57BL/6 mice [21]. The results contributed to the genotoxicity safety characteri-

zation of hemantane and to the understanding of its interaction with MPTP-induced oxidative DNA damage. The compound has been described as having moderate antiradical activity, consistent with a protective effect against oxidative damage to DNA and other cellular macromolecules.

7. Clinical Evidence Base

7.1 Phase 2 trial in early Parkinson disease

The principal clinical evidence for hemantane is a randomized, double-blind, placebo-controlled Phase 2 trial conducted in Russia, reported as an abstract at the 30th CINP World Congress of Neuropsychopharmacology in 2016 [13].

Study design: Sixty patients with newly diagnosed, untreated Parkinson disease were enrolled and randomized to three groups of 20 patients each: (1) hemantane 25 mg daily for 16 weeks; (2) hemantane 25 mg daily for 4 weeks, then increased to 50 mg daily (25 mg twice daily) for the remaining 12 weeks; and (3) matching placebo for 16 weeks.

Primary endpoints: Unified Parkinson's Disease Rating Scale (UPDRS), including Part III (Motor Examination), and additional rating scales measuring rigidity and motor symptoms.

Efficacy results: The 50 mg daily dose produced superior outcomes. The rigidity index decreased by 41 percent from baseline in the 50 mg group. Significant reductions in UPDRS Part III Motor Examination scores were observed at weeks 8, 12, and 16 compared with placebo. Total UPDRS scores showed significant improvement versus placebo after 16 weeks. The 50 mg group outperformed the 25 mg group on total UPDRS scores, indicating a dose-response relationship. The 25 mg dose produced moderate efficacy consistent with a minimally effective dose.

Safety results: General clinical state, blood pressure, electrocardiogram, blood chemistry, and urinalysis were monitored throughout the study. No dose-limiting toxicity was identified at either the 25 mg or 50 mg daily dose. The abstract does not detail individual adverse events or adverse event rates.

Interpretation: The trial confirmed moderate efficacy of hemantane monotherapy in patients with early Parkinson disease at the 50 mg daily dose and established the safety of both tested doses over 16 weeks of administration. The study is limited by its small sample size (20 patients per arm), single-center or limited-center design, and the absence of a full-length peer-reviewed publication detailing the complete dataset, statistical analysis, and individual adverse event reporting.

7.2 Absence of additional clinical data

No additional clinical trials of hemantane have been reported in the English-language literature. The compound has not been evaluated in Phase 3 registration trials, in comparative trials against established antiparkinsonian agents (levodopa, dopamine agonists, MAO-B inhibitors), or in clinical studies for the analgesic, anti-addictive, or anti-inflammatory applications suggested by the preclinical evidence. The current clinical evidence base is therefore limited to a single small Phase 2 study in early Parkinson disease.

8. Sourcing and Quality Verification

Hemantane is not commercially available as a pharmaceutical product in any jurisdiction. The compound has not received marketing authorization and is not manufactured by commercial pharmaceutical companies for clinical use.

Research-grade hemantane may be available from specialized chemical synthesis laboratories and from selected research chemical suppliers. The compound has been synthesized at the Zakusov Institute of Pharmacology and at affiliated Russian pharmaceutical research organizations. Availability outside Russia is limited and may require custom synthesis.

The synthesis via the Leuckart reaction from commercially available precursors (2-adamantanone and azepane) is technically straightforward and can be conducted by competent medicinal chemistry laboratories with standard equipment and reagents [4]. Custom synthesis from contract research organizations is a viable sourcing strategy for investigators requiring gram-scale quantities.

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

- High-performance liquid chromatography area-percent purity, targeting greater than 98 percent
- Mass spectrometry confirmation of molecular weight (234.21 for the protonated free base $[M+H]^+$)
- 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 for common synthesis solvents

Third-party analytical laboratories provide independent confirmation of vendor certificates of analysis. Because hemantane is not a widely marketed research chemical, lot-to-lot variability may be significant, and on-receipt analytical confirmation is essential for any investigation where dose-response precision is important.

9. Reconstitution and Handling

Hemantane hydrochloride is expected to be soluble in water based on the ionic character of the hydrochloride salt and the general solubility properties of aminoadamantane hydrochlorides. For research applications, the compound is typically supplied as a crystalline powder.

Stock solutions for in vitro work can be prepared in water, normal saline, or dimethyl sulfoxide (DMSO) at concentrations of 10 to 100 mM. For in vivo rodent studies, the compound has been administered intraperitoneally as a solution in normal saline at concentrations sufficient for injection volumes of 0.1 to 0.5 mL [8, 10, 12].

The topical formulation studied in the arthritis model was a 5 percent hemantane gel, indicating compatibility with standard dermatological vehicle formulations [15].

Storage of the solid should be at room temperature or refrigerated (2 to 8 degrees Celsius) in a sealed container protected from moisture. The adamantane cage structure confers chemical stability; degradation under standard laboratory storage conditions is expected to be minimal. Aqueous stock solutions should be prepared fresh or stored at refrigerated conditions and used within 7 to 14 days. Light protection is reasonable practice but may not be essential given the absence of chromophoric functional groups in the molecule.

Aliquoting of stock solutions for single-use is recommended to avoid repeated freeze-thaw cycles, although the simple amine structure suggests reasonable resistance to freeze-thaw degradation.

10. Stack Interactions and Combinations

Hemantane interacts with several drug classes through its multi-target pharmacological profile. Investigators conducting research with hemantane, especially in combination regimens or in animals receiving concurrent pharmacological treatments, should consider:

Other NMDA receptor antagonists: Concurrent use with amantadine, memantine, or ketamine produces additive or potentially synergistic NMDA receptor blockade. The combination may enhance neuroprotection but also increases the risk of NMDA-related adverse effects (confusion, hallucinations, dizziness) at higher combined doses. Amantadine and hemantane have been compared but not formally studied in combination [11, 20].

MAO inhibitors: Hemantane is a weak MAO-B inhibitor. Concurrent use with irreversible MAO-B inhibitors (selegiline, rasagiline) produces complex interactions: hemantane may modify the kinetics of irreversible MAO-B inactivation by selegiline [7]. Concurrent use with nonselective MAO inhibitors is contraindicated due to the risk of hypertensive crisis.

Dopaminergic agents: Concurrent levodopa, dopamine agonists (pramipexole, ropinirole, rotigotine), or other dopamine-enhancing agents produce additive dopaminergic stimulation. This combination is pharmacologically rational for Parkinson disease but may increase the risk of dopaminergic adverse effects (dyskinesia, nausea, orthostatic hypotension). Hemantane has been described as a potential agent for reducing levodopa-induced dyskinesia, suggesting that the combination may have therapeutic value [22].

Serotonergic agents: Hemantane modulates serotonin levels in the striatum [10]. Concurrent use with serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, or other serotonergic agents should be approached with caution, although formal serotonergic interaction studies have not been conducted.

Anti-inflammatory agents: Concurrent use with NSAIDs is pharmacologically rational for inflammatory conditions. Hemantane has demonstrated comparable anti-inflammatory efficacy to diclofenac without the ulcerogenic activity of nonselective COX inhibitors [12, 15]. The combination has not been formally studied but the mechanistic independence (NMDA receptor blockade versus COX inhibition) suggests potential for additive benefit.

Ethanol: Hemantane reduces ethanol consumption in preclinical models [19]. Concurrent ethanol exposure may be associated with altered drug-alcohol interactions through the shared NMDA receptor target. Concurrent use in research settings should be monitored for additive central nervous system depression.

Opioids: Hemantane attenuates morphine withdrawal signs and has been characterized in the context of opioid-aminoadamantane interactions [20, 23]. NMDA receptor antagonists can modulate opioid tolerance, dependence, and withdrawal, and the combination may have both therapeutic (withdrawal attenuation) and safety (respiratory depression risk) implications.

11. Adverse Events and Safety Signal

11.1 Preclinical toxicology

Hemantane has undergone preclinical safety evaluation, including acute toxicity, subchronic toxicity, and reproductive toxicology studies.

Acute toxicity: The LD50 for hemantane is substantially above the therapeutic dose range. At 0.2 LD50, the oral dose in rats is approximately 114 mg/kg, indicating an LD50 of approximately 570 mg/kg and a therapeutic index of approximately 28 to 57 relative to the preclinical efficacy dose of 10 to 20 mg/kg [12]. By comparison, diclofenac at 0.2 LD50 corresponds to 74 mg/kg orally in rats.

Gastrointestinal safety: At 0.2 LD50 (114 mg/kg orally), hemantane did not produce macroscopic lesions of the gastric mucosa in fasted rats, in contrast to diclofenac at 0.2 LD50 (74 mg/kg), which produced multiple gastric mucosal lesions [12]. The absence of ulcerogenic activity is a notable safety advantage for a compound with anti-inflammatory indications.

Reproductive toxicology: The effect of hemantane on generative function and gonad morphology has been evaluated in rats [24]. Specific findings have not been detailed in English-language abstracts.

Genotoxicity: DNA comet assay evaluation in C57BL/6 mice examined the effects of hemantane on DNA integrity in brain structures [21]. The compound has been described as having moderate antiradical activity, which may confer protection against oxidative DNA damage.

11.2 Clinical safety

The Phase 2 clinical trial in 60 patients with early Parkinson disease monitored general clinical state, blood pressure, electrocardiogram, blood chemistry, and urinalysis over 16 weeks of treatment at 25 mg and 50 mg daily doses [13]. No dose-limiting toxicity was identified at either dose. Specific adverse event types, rates, and severity grades have not been reported in the available English-language abstract.

By analogy with the aminoadamantane class, the expected adverse event profile includes central nervous system effects (dizziness, insomnia, confusion, hallucinations at higher doses), gastrointestinal effects (nausea), and cardiovascular effects (orthostatic hypotension). The clinical relevance of these expected effects at hemantane doses of 25 to 50 mg daily is unknown in the absence of detailed adverse event reporting.

11.3 Class-related considerations

The aminoadamantane class has an established safety profile. Amantadine is associated with livedo reticularis, peripheral edema, anticholinergic effects, and (at higher doses or in renal impairment) confusion and hallucinations. Memantine is generally well tolerated, with headache, dizziness, and constipation as the most common adverse effects. Hemantane, with its distinct azepane substituent and different receptor pharmacology profile, may exhibit a qualitatively different adverse event spectrum, but this has not been characterized in large clinical populations.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five structurally or mechanistically related compounds against hemantane, evaluated against five competency standards: novelty, effect size, promising potential, side-effect profile, and overall validation. The five comparators were selected to represent the aminoadamantane class (amantadine, memantine), the broader NMDA receptor antagonist space as applied to Parkinson disease (safinamide as a dual NMDA/MAO-B agent), and related experimental adamantane derivatives (nitromemantine, amantadine sulfate extended-release).

12.1 Amantadine

Mechanism: Low-affinity, noncompetitive NMDA receptor antagonist; enhances dopamine release and inhibits dopamine reuptake; anticholinergic properties. Amantadine is the closest structural comparator to hemantane, sharing the adamantane cage with a 1-amino substituent.

Clinical status: Approved in the United States and globally for Parkinson disease (both early-stage monotherapy and levodopa-adjunct therapy, particularly for the management of levodopa-induced dyskinesia) and for influenza A prophylaxis (largely obsolete due to viral resistance). Extended-release formulations (Gocovri, Osmolex ER) are approved specifically for levodopa-induced dyskinesia in Parkinson disease.

Novelty: Low. Amantadine has been in clinical use since 1968 for Parkinson disease and since 1966 for influenza. The mechanism is well characterized but not novel.

Effect size: Moderate for levodopa-induced dyskinesia (approximately 20 to 40 percent reduction in dyskinesia rating scales in randomized trials). Modest for monotherapy in early Parkinson disease. The Pahwa et al. (2017) pivotal trial of extended-release amantadine demonstrated significant reduction in Unified Dyskinesia Rating Scale scores [25].

Promising potential: Moderate. The compound is clinically established with extended-release reformulations extending its commercial life. Research interest centers on dyskinesia management rather than disease modification.

Side-effect profile: Moderate. Livedo reticularis, peripheral edema, insomnia, hallucinations (particularly in elderly patients and at higher doses), constipation, anticholinergic effects. The adverse event profile is well characterized from decades of clinical use.

Overall validation: High. Amantadine has a multi-decade clinical record, regulatory approval, and a substantial evidence base. It is the benchmark against which hemantane was developed.

Comparison to hemantane: Hemantane was specifically developed to exceed amantadine in antiparkinsonian efficacy and breadth of pharmacological action. Preclinical comparisons suggest hemantane is superior to amantadine in several behavioral paradigms, produces broader dopamine transporter modulation, and is more effective in attenuating morphine withdrawal [2, 11, 20]. Hemantane additionally has characterized MAO-B inhibitory activity and anti-inflammatory effects that amantadine does not possess at comparable potency. The principal disadvantage of hemantane relative to amantadine is the absence of clinical approval, the limited clinical evidence base, and the restricted availability.

12.2 Memantine

Mechanism: Moderate-affinity, noncompetitive, voltage-dependent NMDA receptor channel blocker with faster unblocking kinetics than MK-801 and other high-affinity antagonists. Memantine is the clinically approved NMDA antagonist for Alzheimer disease, approved in the United States (Namenda) and globally.

Clinical status: Approved for moderate-to-severe Alzheimer disease. Not approved for Parkinson disease, although it has been studied in Parkinson disease dementia.

Novelty: Low. Memantine has been clinically available since the early 2000s and the mechanism is thoroughly characterized.

Effect size: Small to moderate for Alzheimer disease cognitive endpoints. Meta-analyses report standardized mean differences of approximately 0.2 to 0.3 on cognitive scales, clinically meaningful but modest [26]. Not characterized in Parkinson

disease motor endpoints comparable to hemantane.

Promising potential: Low for novel indications. The compound is in the late life-cycle with generic competition.

Side-effect profile: Favorable. Headache, dizziness, constipation, and confusion are the principal adverse effects, generally at low rates. The voltage-dependent, moderate-affinity channel-blocking kinetics produce a more favorable safety profile than high-affinity NMDA antagonists.

Overall validation: High for Alzheimer disease. The compound has a large clinical evidence base and regulatory approval.

Comparison to hemantane: Memantine and hemantane share the adamantane cage and the NMDA receptor channel-blocking mechanism. Memantine lacks the MAO-B inhibition, the dopamine transporter modulation, and the anti-inflammatory activity that hemantane possesses. Hemantane is positioned as an antiparkinsonian agent, while memantine is positioned for Alzheimer disease. The two compounds are mechanistically related but clinically non-overlapping in their current development.

12.3 Safinamide

Mechanism: Reversible, selective MAO-B inhibitor with additional sodium channel blocking and glutamate release-inhibiting activity. Safinamide represents a dual-mechanism approach (MAO-B inhibition plus antiglutamatergic activity) that parallels, in a different molecular framework, the dual NMDA/MAO-B activity of hemantane.

Clinical status: Approved in the European Union (2015) and United States (2017) as adjunct therapy to levodopa in mid-to-late-stage Parkinson disease with motor fluctuations (Xadago).

Novelty: Moderate. The dual MAO-B inhibition plus antiglutamatergic mechanism is distinct from the pure MAO-B inhibitors (selegiline, rasagiline) and from the NMDA antagonists (amantadine, memantine).

Effect size: Moderate. The pivotal SETTLE and MOTION trials demonstrated significant increases in daily "on" time (approximately 1 to 1.5 hours) and significant reductions in "off" time compared with placebo [27].

Promising potential: Moderate. The compound is clinically established but is a second- or third-line adjunct to levodopa and faces competition from other MAO-B inhibitors and COMT inhibitors.

Side-effect profile: Favorable. Dyskinesia, nausea, insomnia, and headache are the most common adverse effects, generally mild.

Overall validation: High. Regulatory approval, pivotal Phase 3 trials, and post-marketing experience provide a robust evidence base.

Comparison to hemantane: Safinamide and hemantane share a dual NMDA/glutamatergic plus MAO-B inhibitory profile, although through different molecular mechanisms (safinamide blocks sodium channels and inhibits glutamate release, hemantane blocks the NMDA receptor channel). Safinamide is a substantially more potent MAO-B inhibitor than hemantane (nanomolar versus micromolar Ki). Safinamide has the advantage of clinical approval and a robust Phase 3 evidence base. Hemantane has the advantage of additional dopamine transporter modulation, anti-inflammatory activity, and potential analgesic and anti-addictive applications that safinamide does not possess.

12.4 Nitromemantine (YQW-36)

Mechanism: Site-targeted NMDA receptor antagonist that combines the memantine channel-blocking pharmacophore with a nitro group designed to interact with the redox-sensitive regulatory site on the NMDA receptor GluN1/GluN2A subunit. The compound was developed at the Bhatt/Bhatt and Bhatt/Bhatt and Bhatt laboratory at the Sanford Burnham Prebys Medical Discovery Institute by Stuart Lipton and colleagues as a next-generation, subtype-selective NMDA antagonist with improved therapeutic selectivity [28].

Clinical status: Preclinical. The compound has not entered clinical trials.

Novelty: High. The dual-site targeting (channel block plus redox modulation) and the subtype selectivity represent a meaningfully novel approach to NMDA receptor antagonism.

Effect size: Preclinical data show superior neuroprotection relative to memantine in models of Alzheimer disease and in organotypic hippocampal slice models.

Promising potential: Moderate. The novel mechanism is therapeutically attractive but the compound remains in early preclinical development.

Side-effect profile: Preclinical only. Theoretical advantage of improved selectivity and reduced off-target effects relative to memantine.

Overall validation: Low. Preclinical evidence only.

Comparison to hemantane: Both compounds represent next-generation modifications of the aminoadamantane NMDA antagonist scaffold. Hemantane modifies the scaffold by changing the nitrogen substituent and ring attachment point; nitromemantine modifies the scaffold by adding a site-targeted nitro group. Hemantane has the advantage of clinical data (Phase 2 trial); nitromemantine has the advantage of a more precisely targeted receptor interaction. The two compounds are not competitive (different indications, different development stages) but represent parallel evolutionary approaches from the aminoadamantane starting point.

12.5 Amantadine sulfate extended-release (ADS-5102/Gocovri)

Mechanism: Same active molecule as immediate-release amantadine (NMDA receptor antagonism, dopamine release enhancement), formulated as an extended-release capsule with delayed-onset and extended plasma exposure designed specifically for bedtime dosing to produce peak plasma concentrations in the morning [25].

Clinical status: Approved in the United States (2017) for levodopa-induced dyskinesia in patients with Parkinson disease receiving levodopa-based therapy.

Novelty: Low (same molecule, novel formulation).

Effect size: The EASE LID and EASE LID 3 pivotal trials demonstrated significant reduction in Unified Dyskinesia Rating Scale scores (approximately 20 to 37 percent reduction) [25].

Promising potential: Moderate. Clinically established for the specific indication of levodopa-induced dyskinesia.

Side-effect profile: Hallucinations, dizziness, dry mouth, peripheral edema, constipation, falls. The adverse event rate is higher than for immediate-release amantadine, reflecting the higher and more sustained plasma concentrations achieved by the extended-release formulation.

Overall validation: Moderate to high. Regulatory approval for a specific indication within Parkinson disease.

Comparison to hemantane: Amantadine extended-release and hemantane both target the NMDA receptor channel within the context of Parkinson disease. Amantadine extended-release is approved and available; hemantane is investigational. The comparison highlights the difference between a formulation strategy (extended-release amantadine) and a molecular strategy (hemantane) for improving on the immediate-release amantadine baseline.

12.6 Comparator summary

The five comparator compounds occupy distinct positions in the aminoadamantane and NMDA antagonist pharmacology space. **Amantadine** is the clinically established benchmark against which hemantane was developed; hemantane shows preclinical superiority in several paradigms but lacks clinical validation at scale. **Memantine** shares the NMDA channel-blocking mechanism but is positioned for Alzheimer disease rather than Parkinson disease and lacks the multi-target profile of hemantane. **Safinamide** parallels hemantane's dual NMDA/MAO-B activity through a different molecular framework and has the advantage of clinical approval; hemantane has a broader pharmacological profile encompassing dopamine transporter modulation and anti-inflammatory activity. **Nitromemantine** represents a more precisely targeted approach to NMDA antagonism but remains in early preclinical development. **Amantadine extended-release** demonstrates the formulation optimization strategy for the existing amantadine molecule.

Hemantane occupies a unique position in this comparator landscape: it is the only compound with the combination of NMDA receptor antagonism, MAO-B inhibition, dopamine transporter modulation, dopamine receptor subtype modulation, anti-inflammatory activity, and analgesic activity within a single molecular entity. This multi-target profile is the principal scientific rationale for continued investigation. The principal limitation is the absence of large-scale clinical validation and regulatory approval.

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The compound is not commercially available as a pharmaceutical product. Investigators should obtain analytical confirmation of identity and purity on every lot of research-grade material. The preclinical and clinical evidence reviewed in this monograph should be interpreted in the context of the limited clinical dataset (a single Phase 2 study in 60 patients) and the absence of Phase 3 registration data. All dose ranges cited are from published preclinical and clinical research and do not constitute dosing recommendations.