

RESEARCH MONOGRAPH . COMPOUND PROFILE

Atremorine

A standardized biopharmaceutical extract (E-PodoFavalin-15999) obtained by non-denaturing biotechnological procedures from structural components of Vicia faba L., functioning as a potent dopaminergic enhancer, natural L-DOPA donor, and neuroprotective agent for the prevention and treatment of Parkinsonian disorders, with genotype-dependent catecholaminergic and hormonal modulation.

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ABSTRACT

Atremorine (E-PodoFavalin-15999) is a novel biopharmaceutical product obtained by non-denaturing biotechnological processing of structural components of *Vicia faba* L. (the broad bean or fava bean), developed at the EuroEspes Biomedical Research Center (now International Center of Neuroscience and Genomic Medicine, Bergondo, A Coruna, Spain) under the direction of Ramon Cacabelos for the prevention and treatment of Parkinson's disease (PD) and related dopamine-dependent disorders. Unlike synthetic levodopa (L-DOPA) formulations, Atremorine is a complex bioproduct containing a standardized concentration of approximately 25 mg of natural L-DOPA per gram of product, together with vegetal proteins, unsaturated fatty acids, minerals, vitamins, vegetal fiber, starch, carotenoid pigments, and phytosterols, all of which are proposed to contribute synergistically to its pharmacological activity and to confer neuroprotective properties absent from purified synthetic L-DOPA.

Preclinical studies in cell culture (human neuroblastoma SH-SY5Y cells, hippocampal slices under oxygen-glucose deprivation, striatal slices under 6-hydroxydopamine-induced neurotoxicity) and in animal models (MPTP-induced parkinsonism in mice) have demonstrated that Atremorine protects dopaminergic neurons against neurotoxic insult, inhibits microglial activation, and improves motor function [1, 2, 3]. Clinical studies in over 600 Parkinson's disease patients have confirmed that Atremorine is a potent enhancer of catecholaminergic neurotransmission: a single 5 g oral dose produces a dramatic increase in plasma dopamine

levels within one hour, with over 97 percent of patients responding [4, 5]. In drug-free PD patients, plasma dopamine levels increase from approximately 12 pg/mL to approximately 6,463 pg/mL; in patients receiving conventional antiparkinsonian therapy, dopamine levels increase from approximately 1,322 pg/mL to approximately 16,029 pg/mL, indicating substantial potentiation of conventional dopaminergic pharmacotherapy [5, 6]. The dopamine response is accompanied by significant changes in circulating catecholamines (adrenaline, noradrenaline) and in dopamine-regulated hormones (reductions in prolactin, cortisol, and growth hormone), with no significant effect on serotonin or histamine levels [4].

The variability in the Atremorine-induced dopamine response is highly attributable to pharmacogenetic factors. Polymorphic variants in pathogenic genes (notably APOE), metabolic genes (CYP2D6, CYP2C9, CYP2C19, CYP3A4/5), and neurotransmitter transporter genes (SLC6A3/DAT, SLC6A2/NET, SLC6A4/SERT) exert genotype-dependent effects on the magnitude of the dopamine response [5, 7, 8]. APOE-3 carriers are the best responders and APOE-4 carriers are the worst; CYP2D6 normal metabolizers respond most strongly and CYP2D6 poor metabolizers respond least [5, 7]. Atremorine also exerts epigenetic activity, increasing global DNA methylation in both transgenic Alzheimer's disease mice (3xTg model) and in PD patients, with upregulation of the de novo DNA methyltransferase DNMT3a [9]. The coadministration of Atremorine with conventional antiparkinsonian drugs allows dose reduction of the conventional agents by 25 to 50 percent, with enhancement of clinical benefits and reduction of short- and long-term adverse drug reactions [5, 6]. The compound is covered by European Patent EP3225245A1 and related filings. It is not approved by any

major regulatory authority as a pharmaceutical; it is classified and distributed as a bioproduct or nutraceutical. This monograph reviews the composition, extraction, neuroprotective pharmacology, clinical dopaminergic evidence, pharmacogenomic determinants of response, handling, stack interactions, safety profile, and comparative positioning of Atremorine against five alternative dopaminergic and neuroprotective interventions for Parkinson's disease.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Product name: Atremorine.

Development code: E-PodoFavalin-15999. The development code is the canonical identifier in the primary research literature and the identifier under which the compound was characterized in preclinical neuroprotection studies and clinical pharmacogenomic trials at the EuroEspes Biomedical Research Center [1, 4, 5].

Chemical Abstracts Service registry number: Not assigned to the bioproduct as a whole. Atremorine is a standardized multi-component extract, not a single chemical entity. The principal active constituent, L-3,4-dihydroxyphenylalanine (L-DOPA, levodopa), carries CAS registry number 59-92-7.

International Union of Pure and Applied Chemistry name (principal active constituent): (S)-2-amino-3-(3,4-dihydroxyphenyl)propanoic acid. This is the IUPAC designation for L-DOPA, the primary dopaminergic active component of the extract at a standardized concentration of approximately 25 mg per gram of Atremorine product.

Patent identifiers: European Patent EP3225245A1 ("Bioactive extract obtained from *Vicia faba* and its use in the treatment and/or prevention of neurodegenerative diseases"), inventor Ramon Cacabelos Garcia, assignee Eurospes SA [10]. Related patent filings cover the non-denaturing extraction process and the therapeutic applications in neurodegenerative disorders.

Regulatory classification: Atremorine is not classified as a pharmaceutical drug product by the United States Food and Drug Administration, the European Medicines Agency, or other major regulatory authorities. It is distributed as a bioproduct or nutraceutical under the regulatory frameworks applicable in the jurisdictions of distribution. Investigators should be aware that this classification affects both sourcing and the regulatory requirements for any human research application.

1.2 Structural class and chemistry

Atremorine is not a single-entity chemical compound but rather a standardized biopharmaceutical extract derived from structural components (pods) of *Vicia faba* L. (Fabaceae), a leguminous plant species widely cultivated as a food crop. The extraction procedure, described in patent EP3225245A1, employs non-denaturing biotechnological processes designed to preserve the native conformation and bioactivity of the constituent molecules [10].

Principal active constituent: L-DOPA (levodopa), present at approximately 25 mg per gram of finished product. L-DOPA has a molecular formula of $C_9H_{11}NO_4$, an exact mass of 197.0688 g/mol, and a molecular weight of 197.19 g/mol. It is a white to off-white crystalline amino acid, freely soluble in dilute acid and sparingly soluble in water at neutral pH.

Additional constituents (as characterized in published analyses): Vegetal proteins (amino acid composition not fully published); unsaturated fatty acids; minerals (including iron, zinc, magnesium, and potassium); vitamins (including ascorbic acid, tocopherols, and B-group vitamins); vegetal fiber; starch; vegetal pigments (carotenoids); and vegetal sterols (phytosterols, including beta-sitosterol and stigmasterol) [4, 5]. The relative proportions of these constituents have not been published in full quantitative detail in the peer-reviewed literature, though the L-DOPA content has been consistently reported at approximately 25 mg/g across multiple publications.

Source material: *Vicia faba* L. pods from a specific genetic variety (the "genetic species" designation used in the Cacabelos publications suggests a proprietary cultivar or defined genetic line, though the specific variety has not been disclosed publicly) [5].

Physical properties of the finished product: Fine powder, light brown to tan in color, with characteristic vegetal odor. Soluble in water and in dilute acid; the L-DOPA component is extracted into aqueous solution on reconstitution.

1.3 Extraction and preparation

The published extraction procedure is protected by patent and is described in general terms. Structural components of *Vicia faba* L. (principally the pods, which contain the highest concentration of L-DOPA in the plant after the seeds) are processed using non-denaturing biotechnological procedures that preserve the native molec-

ular conformations of proteins, lipids, and small molecules [10]. The process avoids high-temperature denaturation, organic solvent extraction, and harsh chemical treatment. The resulting product is dried, standardized for L-DOPA content (target approximately 25 mg/g), and packaged for distribution.

The non-denaturing extraction is proposed as a critical differentiator from crude *Vicia faba* preparations and from synthetic L-DOPA: the preservation of native protein conformation, the retention of the full complement of plant-derived bioactive molecules, and the standardization of L-DOPA content together produce a bioproduct with neuroprotective and anti-inflammatory properties not present in purified L-DOPA alone [1, 2, 5].

2. Abstract

Atremorine (E-PodoFavalin-15999) is a standardized biopharmaceutical extract of *Vicia faba* L. structural components that functions as a potent natural L-DOPA donor and dopaminergic neuroprotective agent. Developed at the EuroEspes Biomedical Research Center by Ramon Cacabelos and colleagues, the compound has been characterized in preclinical neuroprotection models and in clinical pharmacogenomic studies involving over 600 Parkinson's disease patients [1, 4, 5, 6].

The compound is distinguished from synthetic levodopa and from crude *Vicia faba* preparations by its standardized multi-component composition, its non-denaturing extraction process, and its demonstrated neuroprotective activity in dopaminergic neuronal models. Preclinical studies have demonstrated protection of SH-SY5Y human neuroblastoma cells against MPP⁺ toxicity, protection of hippocampal slices against oxygen-glucose deprivation, protection of striatal slices against 6-hydroxydopamine (6-OHDA) neurotoxicity, and protection against MPTP-induced dopaminergic neurodegeneration in mice with concomitant inhibition of microglial activation and improvement in motor function [1, 2, 3].

Clinical studies demonstrate that a single oral dose of 5 g of Atremorine produces a dramatic and rapid (within one hour) increase in plasma dopamine levels in over 97 percent of PD patients. The magnitude of the dopamine response varies substantially with pharmacogenetic factors, principally APOE genotype, CYP2D6 metabolizer status, and polymorphisms in neurotransmitter transporter genes (SLC6A3, SLC6A2, SLC6A4) [5, 7, 8]. The response is accompanied by increases in circulating catecholamines (noradrenaline, adrenaline), decreases in dopamine-inhibited hormones (prolactin, growth hormone, cortisol), and no significant effect on serotonin or histamine [4].

Coadministration of Atremorine with conventional antiparkinsonian drugs (levodopa/carbidopa, dopamine agonists, MAO-B inhibitors) allows reduction of conventional drug doses by 25 to 50 percent while enhancing clinical benefit and reducing adverse drug reactions [5, 6]. Atremorine also regulates epigenetic processes, increasing global DNA methylation and DNMT3a expression in both transgenic Alzheimer's disease mice and in PD patients [9].

The compound is covered by European patent EP3225245A1 and is distributed as a bioproduct. It has not received regulatory approval as a pharmaceutical drug product from any major regulatory authority. Investigators considering Atremorine for research applications should verify L-DOPA content on every lot and should consider the pharmacogenomic determinants of response as essential elements of study design.

3. Discovery and Development History

3.1 Origin

Atremorine was developed at the EuroEspes Biomedical Research Center (now the International Center of Neuroscience and Genomic Medicine) in Bergondo, A Coruna, Spain, under the scientific direction of Ramon Cacabelos [5]. The EuroEspes group had maintained a long-standing research program in pharmacogenomics and personalized medicine for neurodegenerative disorders, and the development of Atremorine arose from the intersection of this pharmacogenomic expertise with the ethnopharmacological observation that *Vicia faba* consumption was associated with reduced Parkinson's disease symptoms in traditional Mediterranean populations.

3.2 Ethnobotanical and pharmacological background

The broad bean (*Vicia faba* L.) was identified as a natural source of L-DOPA by Markus Guggenheim in 1913, who first isolated L-DOPA from *Vicia faba* seeds [11]. The therapeutic potential of L-DOPA for Parkinson's disease was established through the landmark clinical work of Birkmayer and Hornykiewicz (1961) and Cotzias et al. (1967, 1969), leading to the development of synthetic levodopa as the gold-standard pharmacotherapy for PD [12, 13]. The observation that consumption of fava beans could improve parkinsonian symptoms led to investigation of *Vicia faba* as a dietary and nutraceutical source of L-DOPA, parallel to similar investigations of *Mucuna pruriens* (velvet bean), another L-DOPA-rich legume [14].

3.3 Development of the non-denaturing extraction process

The Cacabelos group recognized that crude *Vicia faba* preparations suffered from inconsistent L-DOPA content, the presence of potentially toxic anti-nutritional factors (vicine, convicine, tannins), and the absence of standardization. The development of a proprietary non-denaturing biotechnological extraction process, designed to produce a standardized product with consistent L-DOPA content (approximately 25 mg/g) while preserving the bioactive co-constituents, was the central

technical innovation underlying Atremorine [5, 10]. The process was patented under European Patent EP3225245A1 (filed 2016, published 2017), with Ramon Cacabelos Garcia as inventor and Euroesperes SA as assignee [10].

3.4 Preclinical neuroprotection program

The initial preclinical characterization of Atremorine focused on neuroprotective activity in dopaminergic neuronal models. Studies conducted at EuroEsperes and at collaborating institutions demonstrated protection in SH-SY5Y human neuroblastoma cells (a standard dopaminergic cell model), in hippocampal slice preparations, in striatal slice preparations under neurotoxic challenge, and in the MPTP mouse model of Parkinson's disease [1, 2, 3]. The neuroprotective activity was characterized as exceeding what would be predicted from the L-DOPA content alone, supporting the hypothesis that the co-constituents of the extract contribute synergistically to the pharmacological effect.

3.5 Clinical pharmacogenomic program

Beginning approximately 2014, the Cacabelos group initiated a systematic clinical program to characterize the dopaminergic response to Atremorine in PD patients and to define the pharmacogenomic determinants of that response. The principal publications from this program appeared between 2016 and 2021 and encompass studies of neurotransmitter and hormonal responses (2016), pharmacogenetics of the dopamine response with respect to CYP and APOE genotypes (2017), transporter gene pharmacogenetics (2021), epigenetic effects (2020), and a comprehensive review integrating neuroprotection and pharmacogenomics (2021) [4, 5, 6, 7, 8, 9]. The clinical program has studied over 600 PD patients and represents the largest systematic pharmacogenomic characterization of any Vicia faba-derived intervention for Parkinson's disease.

3.6 Current development status

Atremorine is distributed as a bioproduct (nutraceutical) through EuroEsperes-affiliated channels. It has not entered the conventional pharmaceutical registration pathway (Phase 1 through Phase 3 clinical trials as required by the FDA, EMA, or equivalent authorities) and is not approved as a drug product in any jurisdiction. The evidence base consists of open-label clinical pharmacogenomic studies rather than randomized, double-blind, placebo-controlled efficacy trials. No active IND

(Investigational New Drug) or CTA (Clinical Trial Application) filings for Atremorine have been publicly disclosed as of the most recent monograph revision.

4. Mechanism of Action

Atremorine exerts its pharmacological effects through multiple convergent mechanisms: direct dopamine precursor supply via its L-DOPA content, neuroprotection of dopaminergic neurons through anti-inflammatory and antioxidant activities attributable to the multi-component extract, and epigenetic modulation of DNA methylation. These mechanisms are described separately below, though they are proposed to operate synergistically in the clinical setting.

4.1 L-DOPA donor activity

The primary acute pharmacological mechanism of Atremorine is the delivery of natural L-DOPA to the systemic circulation. Each gram of Atremorine contains approximately 25 mg of L-DOPA; a standard clinical dose of 5 g therefore delivers approximately 125 mg of L-DOPA [4, 5]. L-DOPA is the immediate biosynthetic precursor of dopamine, converted by the enzyme aromatic L-amino acid decarboxylase (AADC, also known as DOPA decarboxylase) in both central and peripheral tissues. In the context of Parkinson's disease, where dopaminergic neurons in the substantia nigra pars compacta are progressively lost, exogenous L-DOPA replenishes striatal dopamine stores and restores dopaminergic neurotransmission across the nigrostriatal pathway [12, 13].

The clinical observation that Atremorine produces a substantially greater and more rapid dopamine response than would be predicted from its L-DOPA content alone has been noted in multiple publications [4, 5, 6]. Potential explanations include: (a) the presence of endogenous decarboxylase inhibitor-like compounds in the extract that reduce peripheral L-DOPA metabolism, thereby increasing central L-DOPA delivery; (b) synergistic effects of co-constituent antioxidants and anti-inflammatory agents on AADC activity and dopamine release; and (c) neuroprotective preservation of remaining dopaminergic neurons, thereby increasing the efficiency of L-DOPA conversion to dopamine. The relative contribution of these mechanisms has not been definitively established.

4.2 Catecholaminergic neurotransmitter modulation

Beyond the dopamine response, Atremorine administration produces significant increases in circulating noradrenaline and adrenaline levels, consistent with enhanced catecholaminergic neurotransmission [4]. Dopamine serves as the biosynthetic precursor for noradrenaline (via dopamine beta-hydroxylase) and subsequently for adrenaline (via phenylethanolamine N-methyltransferase); elevation of dopamine substrate availability through L-DOPA supplementation predictably increases downstream catecholamine synthesis. Serotonin and histamine levels are not significantly affected by Atremorine, indicating selectivity for catecholaminergic pathways [4].

4.3 Hormonal modulation

The dopamine response to Atremorine produces secondary hormonal effects mediated by dopaminergic regulation of pituitary and adrenal function [4]. Specifically:

- **Prolactin:** Dopamine is the principal tonic inhibitor of prolactin secretion from lactotroph cells of the anterior pituitary (via D2 receptors on lactotrophs). Atremorine-induced dopamine elevation produces significant reduction in circulating prolactin levels, consistent with enhanced dopaminergic inhibition of prolactin secretion.
- **Growth hormone:** Dopamine modulates growth hormone secretion through complex hypothalamic-pituitary interactions. Atremorine administration produces significant reduction in circulating growth hormone levels.
- **Cortisol:** Atremorine produces a modest but significant reduction in circulating cortisol, potentially reflecting dopaminergic modulation of hypothalamic-pituitary-adrenal axis activity or direct anti-stress effects of the extract constituents.

These hormonal responses are consistent with the pharmacological effects of L-DOPA administration and support the clinical observation that Atremorine enhances central and peripheral catecholaminergic neurotransmission.

4.4 Neuroprotection

The neuroprotective activity of Atremorine extends beyond what is attributable to L-DOPA supplementation and is proposed to arise from the multi-component composition of the extract. Preclinical studies have demonstrated the following neuro-

protective activities [1, 2, 3]:

- **In vitro neuroprotection:** Atremorine protects SH-SY5Y human neuroblastoma cells (a standard dopaminergic neuronal model) against MPP⁺-induced cytotoxicity. MPP⁺ is the active metabolite of MPTP and selectively destroys dopaminergic neurons through inhibition of mitochondrial complex I. Atremorine treatment preserves cell viability and mitochondrial function in a concentration-dependent manner.
- **Hippocampal slice protection:** Atremorine protects hippocampal slice preparations against oxygen-glucose deprivation (OGD), a model of ischemic neuronal injury. The protection involves preservation of neuronal viability and attenuation of excitotoxic cascades.
- **Striatal slice protection:** Atremorine protects striatal slice preparations against 6-OHDA-induced neurotoxicity. 6-OHDA is a hydroxylated dopamine analog that selectively destroys catecholaminergic neurons through oxidative stress and mitochondrial dysfunction.
- **In vivo MPTP model:** Atremorine protects against MPTP-induced dopaminergic neurodegeneration in mice when administered either preventively (before MPTP challenge) or therapeutically (after MPTP-induced lesion). The protection includes preservation of tyrosine hydroxylase-positive neurons in the substantia nigra, inhibition of MPTP-induced microglial activation and neuroinflammation, and improvement of motor function as assessed by behavioral testing [2, 3].

The proposed neuroprotective mechanisms include: antioxidant activity (from carotenoids, tocopherols, ascorbic acid, and polyphenolic compounds in the extract); anti-inflammatory activity (suppression of microglial activation and proinflammatory cytokine release); and neurotrophic support (from protein and lipid components that may promote neuronal survival signaling). The relative contribution of individual co-constituents to the overall neuroprotective effect has not been established through systematic fractionation studies.

4.5 Epigenetic modulation

Atremorine regulates DNA methylation in neurodegenerative disorder contexts [9]. In the 3xTg transgenic mouse model of Alzheimer's disease, Atremorine treatment increased global DNA methylation and produced high expression of the de novo DNA methyltransferase DNMT3a. In blood samples from PD patients, Atremorine

treatment also increased global DNA methylation levels. The epigenetic activity is proposed to represent a disease-modifying mechanism distinct from the acute dopamine-enhancing effect, potentially modulating the expression of genes involved in neurodegeneration, neuroinflammation, and neuronal survival [9].

The pharmacogenetic response to the epigenetic effects of Atremorine varies across genophenotypes of cytochrome P450 oxidases (CYP2D6, CYP2C19, CYP2C9, CYP3A4, CYP3A5, CYP1A2), N-acetyltransferase 2 (NAT2), vitamin K epoxide reductase complex subunit 1 (VKORC1), and ATP-binding cassette transporter B1 (ABCB1) [9].

5. Pharmacokinetics

5.1 Absorption

The pharmacokinetics of Atremorine have been characterized indirectly through measurement of plasma dopamine and catecholamine levels rather than through direct measurement of L-DOPA plasma concentrations following Atremorine administration. The standard clinical protocol uses a single oral dose of 5 g of Atremorine powder, and plasma samples are collected at baseline and at one hour post-administration [4, 5].

The L-DOPA component of Atremorine (approximately 125 mg per 5 g dose) is absorbed from the gastrointestinal tract through the large neutral amino acid transporter system (LAT1/SLC7A5), the same transporter system that mediates absorption of synthetic L-DOPA. Oral bioavailability of L-DOPA from Atremorine has not been directly compared to synthetic L-DOPA in a formal pharmacokinetic crossover study, but the clinical observation of robust plasma dopamine elevation within one hour suggests efficient gastrointestinal absorption.

The presence of dietary proteins and amino acids in the Atremorine extract could theoretically compete with L-DOPA for absorption through LAT1, analogous to the well-characterized protein-meal effect on synthetic L-DOPA absorption. However, the clinical data demonstrating consistent and substantial dopamine elevation suggest that this competition, if present, does not meaningfully impair L-DOPA absorption from the Atremorine matrix.

5.2 Metabolism

The L-DOPA component of Atremorine is metabolized through the standard pathways for L-DOPA: peripheral decarboxylation by AADC to dopamine; O-methylation by catechol-O-methyltransferase (COMT) to 3-O-methyldopa; and oxidative deamination of resulting catecholamine metabolites by monoamine oxidase (MAO). In the absence of a peripheral AADC inhibitor (carbidopa, benserazide), the majority of orally administered L-DOPA is decarboxylated peripherally, with only approximately 1 to 5 percent of the dose reaching the central nervous system [12].

Atremorine is administered without a peripheral decarboxylase inhibitor. The resulting pharmacokinetic profile therefore features extensive peripheral conversion of L-DOPA to dopamine, which accounts for the dramatic elevation of plasma dopamine levels observed in clinical studies. The central nervous system delivery of L-DOPA from Atremorine is presumably similar to that of synthetic L-DOPA administered without decarboxylase inhibition, though this has not been directly measured.

The variability in the dopamine response to Atremorine is substantially attributable to pharmacogenetic variation in the enzymes that metabolize L-DOPA and its products. CYP2D6 metabolizer status influences the metabolism of dopamine and its metabolites; CYP2C9, CYP2C19, and CYP3A4/5 polymorphisms influence the metabolism of other bioactive components of the extract [5, 7]. APOE genotype, though not a metabolic enzyme, exerts independent effects on the dopamine response through mechanisms that may involve modulation of neuronal dopamine handling, lipid metabolism, or neuroinflammatory state [5, 7].

5.3 Distribution

Formal distribution studies (volume of distribution, tissue partitioning, blood-brain barrier penetration) have not been published for Atremorine as a composite product. The distribution of the L-DOPA component follows the well-characterized pharmacokinetics of synthetic L-DOPA: the compound distributes into extracellular fluid, crosses the blood-brain barrier through the LAT1 transporter system, and is taken up by surviving dopaminergic neurons in the striatum, where it is decarboxylated to dopamine and stored in synaptic vesicles.

5.4 Elimination

Elimination of the L-DOPA component follows the standard pathways: metabolites of dopamine (homovanillic acid, dihydroxyphenylacetic acid, 3-methoxytyramine) and of 3-O-methyldopa are excreted renally. The plasma half-life of L-DOPA from Atremorine has not been independently characterized; the plasma half-life of synthetic L-DOPA (approximately 1 to 2 hours without decarboxylase inhibition, 1.5 to 3 hours with carbidopa) provides a reasonable estimate.

5.5 Routes of administration

Atremorine is administered exclusively by the oral route. The standard dose in published clinical studies is 5 g of powder, administered as a single dose [4, 5, 6]. Optimal doses are reported to range from 5 to 20 g per day, depending on disease severity and concomitant medication [5, 6]. The powder can be reconstituted in water or taken directly. No parenteral, sublingual, transdermal, or inhaled formulations have been described.

5.6 Special populations

Pharmacokinetic data in special populations (pediatric, geriatric, renal impairment, hepatic impairment) have not been published for Atremorine. Given that the compound is administered as a nutraceutical to a population predominantly comprising elderly patients with Parkinson's disease, age-related pharmacokinetic considerations (reduced renal clearance, altered hepatic metabolism, changes in body composition) are relevant to dose selection and are addressed implicitly through the pharmacogenomic stratification of the clinical data.

6. Preclinical Pharmacology

6.1 In vitro neuroprotection

Atremorine has been evaluated in three principal in vitro neuroprotection models [1, 2]:

SH-SY5Y human neuroblastoma cells. Treatment with Atremorine protected SH-SY5Y cells against MPP⁺-induced cytotoxicity in a concentration-dependent manner. Cell viability, mitochondrial membrane potential, and markers of oxidative stress were preserved in Atremorine-treated cells relative to vehicle-treated controls. The protective effect exceeded that of equivalent concentrations of synthetic L-DOPA, suggesting a contribution from the non-L-DOPA components of the extract.

Hippocampal slice preparations. Atremorine protected hippocampal slices against oxygen-glucose deprivation (OGD), preserving neuronal viability and electrophysiological function. The OGD model simulates ischemic injury and tests both immediate neuroprotective mechanisms and longer-term effects on excitotoxic cascades.

Striatal slice preparations. Atremorine protected striatal tissue slices against 6-OHDA-induced neurotoxicity, demonstrating selective protection of catecholaminergic neurons in the tissue preparation most relevant to Parkinson's disease neuropathology.

6.2 In vivo neuroprotection (MPTP model)

The MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) mouse model is the standard acute pharmacological model of Parkinson's disease, producing selective destruction of dopaminergic neurons in the substantia nigra and consequent depletion of striatal dopamine. Atremorine was evaluated in both preventive and therapeutic protocols [2, 3]:

Preventive protocol. Atremorine administered before MPTP challenge reduced the loss of tyrosine hydroxylase-positive (TH⁺) neurons in the substantia nigra, preserved striatal dopamine content, and attenuated motor deficits relative to vehicle-

treated MPTP controls.

Therapeutic protocol. Atremorine administered after MPTP-induced lesion partially restored TH⁺ neuron counts, improved striatal dopamine levels, and improved motor performance, suggesting both neuroprotective and neurorestorative activity.

Microglial inhibition. Atremorine inhibited MPTP-induced microglial activation in the substantia nigra, reducing expression of microglial markers (Iba-1) and proinflammatory mediators. The inhibition of microglial activation is consistent with an anti-neuroinflammatory mechanism that complements the direct neuroprotective activity [2, 3].

6.3 Epigenetic effects in transgenic models

In the 3xTg transgenic mouse model of Alzheimer's disease (expressing mutant human APP, presenilin-1, and tau), Atremorine treatment increased global DNA methylation and upregulated DNMT3a expression [9]. While this model is not directly relevant to Parkinson's disease, the demonstration of epigenetic modulation in a neurodegenerative context supports the hypothesis that Atremorine may exert disease-modifying effects beyond acute dopamine supplementation.

7. Clinical Evidence Base

7.1 Overview of the clinical program

The clinical evidence base for Atremorine consists of open-label pharmacogenomic studies conducted at the EuroEspes Biomedical Research Center and the International Center of Neuroscience and Genomic Medicine in Bergondo, Spain, under the direction of Ramon Cacabelos [4, 5, 6, 7, 8, 9]. The program has enrolled over 600 PD patients and has characterized the dopaminergic, catecholaminergic, hormonal, and epigenetic responses to Atremorine in relation to a comprehensive panel of pharmacogenomic markers. The studies are open-label and are not randomized, double-blind, or placebo-controlled; the evidence should therefore be interpreted with the limitations inherent to this study design.

7.2 Neurotransmitter and hormonal response study (2016)

The foundational clinical publication characterized the neurotransmitter and hormonal response to Atremorine in 119 Parkinson's disease patients [4]. Patients received a single oral dose of 5 g of Atremorine, and plasma levels of dopamine, noradrenaline, adrenaline, serotonin, histamine, ACTH, growth hormone, prolactin, FSH, LH, cortisol, estrogens, and testosterone were measured at baseline and at one hour post-administration.

Dopamine response. Plasma dopamine levels increased from 762.28 plus or minus 296.94 pg/mL at baseline to 4,556.61 plus or minus 678.95 pg/mL at one hour (p less than 0.001), representing an approximately 6-fold increase in the full cohort [4].

Catecholamine response. Noradrenaline and adrenaline levels increased significantly. Serotonin and histamine levels did not change significantly.

Hormonal response. Prolactin, growth hormone, and cortisol levels decreased significantly, consistent with enhanced dopaminergic inhibition of pituitary hormone secretion. ACTH, FSH, LH, estrogen, and testosterone responses were variable.

7.3 Pharmacogenetics of the dopamine response (2017)

The pharmacogenetic characterization of the Atremorine-induced dopamine response was published in 2017, analyzing data from a larger patient cohort [5, 7]. The principal findings were:

APOE genotype. APOE-3/3 carriers showed the strongest dopamine response; APOE-4 carriers showed a significantly attenuated response; APOE-2 carriers showed an intermediate-to-strong response [5, 7].

CYP2D6 metabolizer status. Normal metabolizers (extensive metabolizers) showed the strongest dopamine response; poor metabolizers showed a significantly weaker response. Intermediate and ultrarapid metabolizer phenotypes showed responses between these extremes [5, 7].

CYP2C9, CYP2C19, CYP3A4/5 genotypes. Polymorphisms in these cytochrome P450 enzymes exerted additional, independent effects on the magnitude of the dopamine response [5, 7].

7.4 Drug-free versus treated patients

A particularly notable finding of the clinical program is the differential response in drug-free PD patients versus patients receiving conventional antiparkinsonian drugs [5, 6]:

Drug-free patients. Baseline plasma dopamine levels were extremely low (12.14 plus or minus 0.34 pg/mL), consistent with severe dopaminergic deficiency. After a single 5 g oral dose of Atremorine, dopamine levels increased to 6,463.21 plus or minus 1,306.90 pg/mL, representing an approximately 530-fold increase.

Patients on conventional antiparkinsonian drugs. Baseline plasma dopamine levels were higher (1,321.53 plus or minus 389.94 pg/mL), reflecting the effects of levodopa/carbidopa, dopamine agonists, and other agents. After Atremorine administration, dopamine levels increased to 16,028.54 plus or minus 4,783.98 pg/mL, representing an approximately 12-fold increase from the already elevated baseline.

These data indicate that Atremorine potentiates the dopaminergic effects of conventional antiparkinsonian drugs. The clinical observation that coadministration allows a 25 to 50 percent reduction in conventional drug doses, with preservation

or enhancement of clinical benefit and reduction of adverse drug reactions, represents the most translationally significant finding of the clinical program [5, 6].

7.5 Neurotransmitter transporter pharmacogenetics (2021)

The influence of genetic variation in neurotransmitter transporter genes on the Atremorine-induced dopamine response was characterized in a 2021 publication [8]. Polymorphisms in the dopamine transporter gene (SLC6A3/DAT; rs460000), the noradrenaline transporter gene (SLC6A2/NET; rs12708954, rs3785143, rs5569), and the serotonin transporter gene (SLC6A4/SERT; rs2020934, rs2020936, rs4251417, rs6354) exerted genotype-dependent effects on the magnitude of the dopamine response, with potential impact on the pharmacogenetic outcome and minimal effects on noradrenaline and serotonin levels [8].

7.6 Epigenetic clinical effects (2020)

In PD patients, Atremorine treatment increased global DNA methylation levels in blood samples, paralleling the epigenetic effects observed in the 3xTg transgenic mouse model [9]. The DNA methylation response varied across pharmacogenetic genophenotypes, including CYP2D6, CYP2C19, CYP2C9, CYP3A4, CYP3A5, CYP1A2, NAT2, VKORC1, ABCB1, and SLCO1B1 [9].

7.7 Comprehensive review (2021)

The 2021 review by Cacabelos in Medicinal Research Reviews integrated the full body of preclinical and clinical evidence for Atremorine, spanning dopaminergic neuroprotection, clinical pharmacology, and pharmacogenomics [5]. The review reported that over 97 percent of PD patients respond to a single dose of Atremorine (5 g oral), and that optimal doses range from 5 to 20 g per day depending on disease severity and concomitant medications. The review also reported that Atremorine coadministration allows dose reduction of conventional antiparkinsonian drugs by 25 to 50 percent.

7.8 Limitations of the clinical evidence

The clinical evidence for Atremorine has several important limitations that investigators should consider:

- All published clinical studies are open-label and uncontrolled; no randomized, double-blind, placebo-controlled trials of Atremorine efficacy in Parkinson's disease have been published.
- The clinical endpoint (plasma dopamine level) is a pharmacodynamic biomarker, not a clinical outcome measure. Sustained motor improvement, Activities of Daily Living scores, Unified Parkinson's Disease Rating Scale (UPDRS) scores, and long-term disease modification endpoints have not been formally evaluated in controlled trials.
- The clinical program has been conducted exclusively at institutions affiliated with the EuroEspes/Cacabelos research group. Independent replication by unaffiliated investigators has not been published.
- The regulatory classification of Atremorine as a bioproduct/nutraceutical, rather than a pharmaceutical drug product, reflects the absence of the regulatory-quality clinical trials that would be required for drug approval.

8. Sourcing and Quality Verification

Atremorine is available through EuroEspes Biotechnology (Euroespes SA) and affiliated distribution channels. It is supplied as a standardized powder with an L-DOPA content of approximately 25 mg per gram of product [5]. The compound is not listed in standard chemical research supplier catalogs (Sigma-Aldrich, Tocris, Cayman Chemical, MedChemExpress, Selleckchem) and is not available as a research-grade single-entity chemical.

Investigators obtaining Atremorine should perform the following quality verifications on each lot:

- **L-DOPA content determination.** High-performance liquid chromatography (HPLC) with ultraviolet detection at 280 nm, using a certified L-DOPA reference standard (Sigma-Aldrich catalog number D9628 or equivalent). The target L-DOPA content is approximately 25 mg/g; deviation of more than 20 percent from this specification should prompt rejection of the lot or dose adjustment.
- **Anti-nutritional factor screening.** *Vicia faba* contains the pyrimidine glycosides vicine and convicine, which are hydrolyzed in vivo to the aglycones divicine and isouramil. These aglycones cause oxidative hemolytic anemia in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency (favism). Investigators should confirm that vicine and convicine levels are below quantification limits or are at levels consistent with safe consumption [15].
- **Microbial testing.** Total aerobic microbial count, yeast and mold count, and absence of specific pathogens (*Salmonella*, *Escherichia coli*, *Staphylococcus aureus*) per pharmacopoeial standards for botanical products.
- **Heavy metal screening.** Arsenic, cadmium, lead, and mercury testing by inductively coupled plasma mass spectrometry (ICP-MS) or equivalent, per pharmacopoeial limits for botanical products.
- **Pesticide residue screening.** Multi-residue pesticide analysis per pharmacopoeial standards.
- **Moisture content.** Karl Fischer or loss-on-drying analysis; moisture content should be below 10 percent for stability.

Independent analytical laboratories can provide verification of these parameters. Investigators relying on the vendor certificate of analysis should be aware that third-party verification has not been independently validated in the published literature.

9. Reconstitution and Handling

Atremorine is supplied as a dry powder and does not require reconstitution for oral administration. For research applications requiring aqueous solutions, the following guidelines apply:

Oral administration (clinical/research). The powder (typically 5 g per dose) is administered directly by mouth or suspended in 100 to 200 mL of water immediately before administration. The suspension should be consumed promptly after preparation, as L-DOPA undergoes oxidative degradation in aqueous solution (especially at neutral to alkaline pH and in the presence of dissolved oxygen).

Aqueous stock preparation for in vitro studies. Dissolve the appropriate quantity of Atremorine powder in acidified water (pH 2 to 3, using hydrochloric acid or citric acid) or in phosphate-buffered saline (pH 7.4) with 0.1 percent ascorbic acid as an antioxidant. Filter through a 0.22 micrometer membrane for sterility. Prepare fresh daily; L-DOPA solutions are not stable for extended storage at room temperature or at 4 degrees Celsius without antioxidant protection.

Storage of dry powder. Store at room temperature (15 to 25 degrees Celsius) in a sealed container, protected from moisture and light. The powder is stable under these conditions for the shelf life stated by the manufacturer (typically 24 months from date of manufacture).

Light sensitivity. L-DOPA is sensitive to light-induced oxidation. Amber glass or opaque containers are recommended for storage of both the dry powder and any prepared solutions.

Incompatibilities. L-DOPA is oxidized by ferric iron and by strong oxidizing agents. Avoid contact with iron-containing implements during preparation. L-DOPA chelates divalent metal ions (iron, zinc, copper); co-administration with mineral supplements containing these metals may reduce L-DOPA bioavailability.

10. Stack Interactions and Combinations

Atremorine interacts with several drug classes through its L-DOPA content and through the pharmacogenomic determinants of L-DOPA metabolism. Investigators and practitioners should consider the following interactions:

Peripheral decarboxylase inhibitors (carbidopa, benserazide). Coadministration with a peripheral AADC inhibitor would be expected to increase central L-DOPA delivery from Atremorine by reducing peripheral decarboxylation, analogous to the standard levodopa/carbidopa combination. The published Atremorine studies did not co-administer a decarboxylase inhibitor; the dramatic peripheral dopamine elevation observed reflects uninhibited peripheral decarboxylation. Investigators considering central nervous system endpoints should evaluate whether addition of a decarboxylase inhibitor would improve the therapeutic ratio.

Levodopa/carbidopa (Sinemet, Stalevo) and levodopa/benserazide (Madopar). Atremorine potentiates the dopaminergic effects of conventional levodopa formulations, allowing dose reduction of 25 to 50 percent [5, 6]. However, the total L-DOPA exposure (from Atremorine plus synthetic levodopa) should be monitored to avoid excessive dopaminergic stimulation, which can produce dyskinesias, hallucinations, and orthostatic hypotension.

Dopamine agonists (pramipexole, ropinirole, rotigotine, apomorphine). Additive dopaminergic activity is expected. Dose adjustment of the dopamine agonist may be required to avoid excessive dopaminergic stimulation.

MAO-B inhibitors (selegiline, rasagiline, safinamide). These agents inhibit the degradation of dopamine and thereby potentiate the dopaminergic effects of Atremorine. The combination is pharmacologically rational but increases the risk of hypertensive crisis (the "cheese reaction") if dietary tyramine exposure is concurrent.

COMT inhibitors (entacapone, opicapone, tolcapone). These agents inhibit the O-methylation of L-DOPA to 3-O-methyldopa, increasing L-DOPA bioavailability and extending its duration of action. Coadministration with Atremorine would increase the effective L-DOPA exposure from the extract.

Iron and mineral supplements. L-DOPA chelates divalent metal ions. Concurrent administration with iron, zinc, or copper supplements may reduce L-DOPA absorption. A separation of at least 2 hours between Atremorine and mineral supplements is recommended.

High-protein meals. Dietary large neutral amino acids compete with L-DOPA for absorption through the LAT1 transporter in the intestinal mucosa and at the blood-brain barrier. High-protein meals may reduce L-DOPA absorption from Atremorine. Administration on an empty stomach or with a low-protein meal may optimize absorption.

CYP2D6 inhibitors and inducers. CYP2D6 metabolizer status significantly influences the Atremorine-induced dopamine response [5, 7]. Strong CYP2D6 inhibitors (paroxetine, fluoxetine, bupropion, quinidine) may alter the metabolism of dopamine and other bioactive components of the extract. CYP2D6 inducers may reduce the pharmacological effect.

Antipsychotic drugs. Dopamine receptor antagonists (haloperidol, risperidone, olanzapine, quetiapine, aripiprazole) would be expected to antagonize the dopaminergic effects of Atremorine. Concurrent use is pharmacologically contradictory and should be avoided unless specifically indicated.

Antiemetic drugs with dopamine antagonist activity. Metoclopramide and domperidone are dopamine D2 receptor antagonists used as antiemetics and prokinetics. These agents would antagonize the dopaminergic effects of Atremorine and may exacerbate parkinsonian symptoms.

11. Adverse Events and Safety

11.1 Reported adverse event profile

The published clinical studies of Atremorine have not reported a detailed, systematic adverse event profile comparable to the structured safety reporting required in regulatory-quality clinical trials. The available safety information is limited to general statements in review articles and clinical publications [5, 6].

The Cacabelos 2021 review states that coadministration of Atremorine with conventional antiparkinsonian drugs allows dose reduction of conventional agents by 25 to 50 percent, "with enhancement of clinical benefits, reduction of short- and long-term adverse drug reactions, and extending the therapeutic effect of conventional antiparkinsonian drugs" [5]. This statement implies a favorable safety profile relative to standard-dose conventional therapy, but quantitative adverse event rates, severity grading, and causality assessments have not been published.

11.2 Expected adverse events based on pharmacological mechanism

Given the L-DOPA content and dopaminergic mechanism of Atremorine, the following adverse events would be expected by pharmacological class effect, analogous to those observed with synthetic levodopa:

- **Nausea and vomiting.** L-DOPA stimulates the chemoreceptor trigger zone (area postrema) through dopamine D2 receptors. Nausea is the most common adverse event of levodopa therapy, particularly in the absence of a peripheral decarboxylase inhibitor. Atremorine is administered without carbidopa or benserazide, which would be expected to increase the incidence of nausea relative to standard levodopa/carbidopa combinations.
- **Orthostatic hypotension.** Peripheral dopamine and noradrenaline elevation can produce vasodilation and orthostatic hypotension, especially in elderly patients with autonomic dysfunction.
- **Dyskinesias.** With chronic L-DOPA supplementation, involuntary movements (dyskinesias) can develop, particularly in patients with advanced Parkinson's disease and established levodopa therapy. The risk with Atremorine at typical

doses (5 g, delivering approximately 125 mg L-DOPA) may be lower than with standard levodopa doses (300 to 1,500 mg daily) but cannot be excluded.

- **Psychiatric effects.** Dopaminergic stimulation can produce hallucinations, confusion, and impulse control disorders (compulsive gambling, hypersexuality, compulsive eating, compulsive shopping), particularly in the context of concurrent dopamine agonist therapy.
- **Cardiovascular effects.** Dopamine and catecholamine elevation can produce tachycardia and cardiac arrhythmias in susceptible individuals.

11.3 Favism risk

Vicia faba contains the pyrimidine glycosides vicine and convicine, which can cause acute hemolytic anemia (favism) in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency [15]. G6PD deficiency is the most common human enzyme deficiency, affecting approximately 400 million people worldwide, with highest prevalence in populations of Mediterranean, African, and Southeast Asian descent. Investigators administering Atremorine should screen participants for G6PD deficiency prior to administration or should confirm that the extraction process removes vicine and convicine to below clinically significant levels.

11.4 Drug interaction safety considerations

The potential for pharmacodynamic interactions with conventional antiparkinsonian drugs (additive dopaminergic effects, risk of dyskinesias and psychiatric symptoms) and with MAO inhibitors (hypertensive crisis risk with concurrent tyramine) represents a significant safety consideration for Atremorine use. These interactions are discussed in Section 10.

11.5 Long-term safety

Long-term safety data for Atremorine are not available in the published literature. The longest reported treatment durations in the clinical program have not been specified in the available publications. Long-term safety considerations relevant to chronic L-DOPA supplementation (motor fluctuations, wearing-off phenomena, dyskinesias, psychiatric complications) apply to Atremorine by pharmacological class.

12. Comparative Assessment

This section presents a structured comparative assessment of five alternative dopaminergic or neuroprotective interventions for Parkinson's disease against Atremorine, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five comparators were selected as agents that share relevant mechanistic features with Atremorine or that occupy adjacent therapeutic niches in the management of Parkinson's disease.

12.1 *Mucuna pruriens* (velvet bean extract)

Mechanism: Natural L-DOPA donor from the seeds of *Mucuna pruriens*, a tropical legume. L-DOPA content in seeds is 3 to 6 percent by weight, substantially higher than in *Vicia faba* [14]. The extract also contains other bioactive compounds (including 5-HTP, nicotine, and bufotenine in small quantities) that may modulate the pharmacological response.

Clinical evidence: A landmark crossover study by Katzenschlager et al. (2004) compared *Mucuna pruriens* seed powder (15 g and 30 g, containing approximately 500 mg and 1,000 mg of L-DOPA respectively) with synthetic levodopa/carbidopa (200/50 mg) in 8 PD patients [16]. *Mucuna pruriens* produced comparable motor improvement (UPDRS motor scores), faster onset of action, longer duration of "on" time, and lower peak-dose dyskinesias. Additional clinical studies have confirmed tolerability and efficacy.

Novelty: Low. The concept of natural L-DOPA delivery from leguminous plants is shared with Atremorine. *Mucuna pruriens* has been studied for this application for decades and is the historical comparator for all plant-derived L-DOPA interventions.

Effect size: Moderate. Clinical motor improvement comparable to synthetic levodopa/carbidopa at equivalent L-DOPA doses, with potential advantages in onset time and dyskinesia profile [16].

Promising potential: Moderate. Not approved as a pharmaceutical; available as a dietary supplement. Multiple clinical studies support efficacy. International interest is growing, particularly in resource-limited settings where synthetic levodopa is expensive or unavailable.

Side-effect profile: Similar to synthetic levodopa (nausea, vomiting, orthostatic hypotension), though the Katzenschlager study reported lower dyskinesias. Favism risk is not applicable (*Mucuna pruriens* does not contain vicine/convicine). Contains trace quantities of tryptamines and other alkaloids whose safety profile in chronic use is incompletely characterized.

Overall validation: Moderate. The clinical evidence is stronger than for Atremorine (crossover design against active comparator, UPDRS motor endpoints), though still limited in scale and duration.

Comparison to Atremorine: Both compounds are natural L-DOPA donors from leguminous plants. *Mucuna pruriens* has a higher L-DOPA content per gram and a more developed clinical evidence base with motor endpoints. Atremorine has a more comprehensive pharmacogenomic characterization, demonstrated neuroprotective activity in preclinical models (not established for *Mucuna pruriens* extracts at comparable depth), and the additional epigenetic modulation. Atremorine's non-denaturing extraction process is proposed as a differentiator but has not been compared directly to *Mucuna pruriens* preparations in a head-to-head study.

12.2 Synthetic Levodopa/Carbidopa (Sinemet)

Mechanism: Synthetic L-DOPA combined with the peripheral AADC inhibitor carbidopa. Carbidopa prevents peripheral decarboxylation of L-DOPA, increasing central L-DOPA delivery from approximately 1 to 5 percent (without inhibitor) to approximately 10 to 30 percent and reducing peripheral dopaminergic adverse events (nausea, orthostatic hypotension) [12, 13].

Clinical evidence: Levodopa/carbidopa is the gold-standard pharmacotherapy for Parkinson's disease, supported by over 50 years of clinical use, hundreds of randomized controlled trials, and inclusion in every national and international PD treatment guideline. The evidence base is vast and unequivocal for symptomatic motor benefit.

Novelty: None. Levodopa/carbidopa is the established standard of care.

Effect size: Large. The symptomatic motor benefit of levodopa is the largest of any antiparkinsonian drug, with UPDRS motor improvement of 30 to 50 percent in moderate-to-advanced PD.

Promising potential: Not applicable (already approved and in universal clinical use).

Side-effect profile: Well characterized. Short-term: nausea (reduced by carbidopa), orthostatic hypotension, somnolence. Long-term: motor fluctuations (wearing-off, on-off phenomena), dyskinesias (affecting 40 to 80 percent of patients after 5 to 10 years of therapy), psychiatric effects (hallucinations, impulse control disorders).

Overall validation: Very high. The most extensively validated intervention in the history of Parkinson's disease therapeutics.

Comparison to Atremorine: Atremorine delivers a lower dose of L-DOPA per administration (approximately 125 mg from 5 g versus typical synthetic levodopa doses of 300 to 1,500 mg daily), is administered without a peripheral decarboxylase inhibitor, and has demonstrated neuroprotective activity that synthetic levodopa has not consistently shown. The proposed advantage of Atremorine is the combination of L-DOPA supplementation with neuroprotection and with the synergistic effects of the plant co-constituents; the principal disadvantage is the absence of regulatory-quality controlled clinical trials and the absence of a decarboxylase inhibitor to optimize central L-DOPA delivery.

12.3 Isradipine

Mechanism: Dihydropyridine L-type calcium channel blocker (Cav1.3 selective). The dopaminergic neurons of the substantia nigra pars compacta are unusual in their reliance on L-type calcium channels for autonomous pacemaker activity; this calcium entry contributes to oxidative stress and mitochondrial vulnerability. Isradipine was hypothesized to reduce this vulnerability and provide neuroprotection [17].

Clinical evidence: The STEADY-PD III trial (Bhatt et al. 2020, JAMA Neurology), a Phase 3 randomized, double-blind, placebo-controlled trial of isradipine 10 mg daily in 336 early PD patients over 36 months, showed no significant difference in

UPDRS total score change from baseline between isradipine and placebo [17]. The trial was the largest and most rigorous test of a calcium channel blocker for PD neuroprotection and produced a definitive negative result.

Novelty: Moderate. The calcium channel hypothesis of PD neuroprotection was scientifically novel and well-supported by preclinical evidence.

Effect size: Absent. The Phase 3 trial showed no detectable neuroprotective or symptomatic benefit.

Promising potential: Low. Development for PD neuroprotection has been abandoned following the STEADY-PD III negative result.

Side-effect profile: Well characterized (marketed antihypertensive). Principal effects are peripheral edema, dizziness, headache, and hypotension. The 10 mg PD dose produced higher rates of these effects than the lower antihypertensive doses.

Overall validation: Low for PD neuroprotection. The compound is validated as an antihypertensive but has been definitively shown to lack neuroprotective efficacy in PD at the studied dose.

Comparison to Atremorine: Isradipine was the most rigorously tested neuroprotective candidate for PD (Phase 3, double-blind, placebo-controlled) and produced a definitively negative result. Atremorine has demonstrated neuroprotection in preclinical models but has not been tested in a controlled clinical neuroprotection trial. The comparison illustrates the gap between preclinical neuroprotection (which Atremorine shares with isradipine) and clinical neuroprotection (which neither compound has demonstrated in a controlled setting).

12.4 Inosine (urate elevation strategy)

Mechanism: Oral inosine is a purine nucleoside that elevates circulating urate levels. Epidemiological evidence consistently shows that higher serum urate levels are associated with lower PD risk and slower disease progression. Urate is an antioxidant that may protect dopaminergic neurons against oxidative stress [18].

Clinical evidence: The SURE-PD3 trial (Schwarzschild et al. 2021, JAMA Neurology), a Phase 3 randomized, double-blind, placebo-controlled trial of inosine (dosed to achieve serum urate of 7.1 to 8.0 mg/dL) in 298 early PD patients over 24

months, showed no significant benefit of urate elevation on the rate of clinical decline (change in Movement Disorder Society UPDRS total score) [18]. The trial was terminated early for futility.

Novelty: Moderate. The urate-neuroprotection hypothesis was epidemiologically well-supported and mechanistically plausible.

Effect size: Absent. The Phase 3 trial showed no detectable benefit.

Promising potential: Low. The neuroprotection strategy based on urate elevation has been abandoned following the SURE-PD3 negative result.

Side-effect profile: Urate elevation carries risk of gout, uric acid nephrolithiasis, and cardiovascular effects in susceptible individuals. These risks were managed in the clinical trial through dose titration.

Overall validation: Low for PD neuroprotection.

Comparison to Atremorine: Like isradipine, inosine illustrates the failure of a well-supported neuroprotection hypothesis to translate from epidemiological and preclinical evidence to clinical benefit in a rigorous Phase 3 trial. Atremorine's pre-clinical neuroprotective evidence must be interpreted in light of these translational failures.

12.5 Exenatide (GLP-1 receptor agonist)

Mechanism: Glucagon-like peptide-1 (GLP-1) receptor agonist, originally developed for type 2 diabetes. GLP-1 receptors are expressed on neurons throughout the brain, including in the substantia nigra. Preclinical studies have demonstrated neuroprotective effects in multiple models of PD, including protection against MPTP and 6-OHDA neurotoxicity, anti-inflammatory activity, and neurotrophic effects [19].

Clinical evidence: The Athauda et al. (2017) randomized, double-blind, placebo-controlled trial of exenatide (2 mg subcutaneous injection once weekly) in 62 moderate PD patients over 48 weeks plus 12 weeks washout showed a significant positive effect on the Movement Disorder Society UPDRS Part 3 (motor) score at 60 weeks [19]. The effect was 3.5 points in favor of exenatide after the 12-week washout, suggesting a disease-modifying rather than purely symptomatic effect. A larger Phase 3 trial is underway.

Novelty: High. GLP-1 receptor agonism as a neuroprotective strategy for PD represents a mechanistically distinct approach from dopamine supplementation.

Effect size: Small to moderate. The 3.5-point difference on MDS-UPDRS Part 3 is clinically modest but statistically significant and, critically, persisted after drug washout [19].

Promising potential: High. Active Phase 3 development; strong mechanistic rationale; favorable safety profile from extensive diabetes use; multiple related GLP-1 agonists (liraglutide, lixisenatide) also under investigation for PD.

Side-effect profile: Well characterized from diabetes use. Principal effects are nausea (common, usually transient), injection-site reactions, and modest weight loss. Serious effects are rare.

Overall validation: Moderate to high. The Phase 2 data are the most encouraging neuroprotection result in PD in recent years. Phase 3 confirmation is awaited.

Comparison to Atremorine: Exenatide and Atremorine both claim neuroprotective activity but operate through entirely different mechanisms (GLP-1 receptor agonism versus multi-component botanical extract with L-DOPA content). Exenatide has a controlled clinical trial demonstrating a potential disease-modifying effect; Atremorine has preclinical neuroprotection data and open-label clinical dopamine enhancement data. Exenatide does not provide dopamine precursor supplementation. The two agents are not directly competitive but illustrate different approaches to the shared goal of neuroprotection in PD.

12.6 Comparator summary

The five comparators span the landscape of dopaminergic supplementation and neuroprotection for Parkinson's disease. **Mucuna pruriens** is the closest mechanistic comparator to Atremorine (natural L-DOPA donor) and has a slightly stronger clinical evidence base for motor endpoints, though without the pharmacogenomic depth of the Atremorine program. **Synthetic levodopa/carbidopa** is the gold-standard symptomatic therapy and the benchmark against which all dopaminergic interventions are measured; Atremorine is not a substitute for levodopa/carbidopa but is proposed as a complementary agent that may allow dose reduction. **Isradipine** and **inosine** represent neuroprotection strategies that were well-supported preclinically but failed definitively in Phase 3 clinical trials, providing a cau-

tionary context for Atremorine's preclinical neuroprotection claims. **Exenatide** is the most scientifically advanced neuroprotection candidate, with Phase 2 evidence of disease modification and active Phase 3 development.

Atremorine occupies a distinctive position in this landscape: it combines L-DOPA supplementation (shared with *Mucuna pruriens* and synthetic levodopa), preclinical neuroprotection (shared, albeit through different mechanisms, with all comparators), pharmacogenomic characterization (unique to Atremorine in depth and breadth), and epigenetic modulation (not demonstrated for any comparator). Its principal limitations are the absence of controlled clinical efficacy trials, the absence of a peripheral decarboxylase inhibitor in the formulation, the single-center provenance of all clinical data, and the nutraceutical rather than pharmaceutical regulatory classification. These limitations place Atremorine in the category of a promising research-stage bioproduct rather than a validated therapeutic intervention. Investigators considering Atremorine for research applications should design pharmacogenomically stratified studies with controlled comparator arms and clinical outcome endpoints to advance the evidence base beyond the current open-label pharmacodynamic data.

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and for G6PD deficiency in study participants, and should design controlled studies with clinical outcome endpoints to advance the evidence base. Compound class generalizations are noted where compound-specific data are sparse; investigators should weight the evidence accordingly.