

RESEARCH MONOGRAPH . COMPOUND PROFILE

Pitolisant

A first-in-class non-imidazole piperidine derivative developed at Bioprojet as a selective histamine H₃ receptor inverse agonist, approved for narcolepsy-associated excessive daytime sleepiness and cataplexy, and distinguished from conventional stimulants by histaminergic wake promotion without dopaminergic reinforcement or controlled-substance classification.

DOCUMENT	KDC-MN-1442
ISSUED	2026-05-11
REVISION	1.0
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COMPOUND CLASS	Histamine H ₃ receptor inverse agonist/antagonist with secondary sigma-1 receptor agonism and wake-promoting eugeroic activity

ABSTRACT

Pitolisant (BF2.649, Wakix) is the first histamine H₃ receptor inverse agonist/antagonist to achieve regulatory approval, authorized by the European Medicines Agency in March 2016 and by the United States Food and Drug Administration in August 2019 for the treatment of excessive daytime sleepiness in adult patients with narcolepsy. The compound is a non-imidazole piperidine derivative, chemically designated 1-{3-[3-(4-chlorophenyl)propoxy]propyl}piperidine hydrochloride, that binds the human histamine H₃ receptor with sub-nanomolar affinity (K_i approximately 0.3 to 1.0 nM) and functions as a potent inverse agonist at the constitutively active receptor with an EC₅₀ of approximately 1.5 nM [1, 2]. By antagonizing presynaptic H₃ autoreceptors on tuberomammillary histaminergic neurons, pitolisant enhances endogenous histamine synthesis and release, thereby activating downstream wake-promoting circuitry including noradrenergic, dopaminergic, and cholinergic projection systems, without direct dopaminergic reinforcement in the nucleus accumbens [3, 4]. This mechanistic distinction from amphetamine, modafinil, and solriamfetol is the pharmacological basis for the compound's classification as a non-controlled substance in both the United States and the European Union, a clinically meaningful regulatory differentiation in a therapeutic area historically dominated by Schedule II and Schedule IV agents. The clinical evidence base for pitolisant in narcolepsy rests on the HARMONY trial program: HARMONY 1 demonstrated statistically significant reduction in Epworth Sleepiness Scale scores versus placebo (Cohen's d 0.61) and significant reduction in weekly cataplexy rate (62% versus 8% for placebo) [5, 6]; HARMONY CTP

confirmed anti-cataplectic efficacy with a Cohen's d of 0.86 and a 75% reduction in weekly cataplexy rate versus 38% for placebo [7]; and HARMONY III established long-term safety and efficacy over 12 months of continuous dosing [8]. The FDA subsequently expanded the indication to include cataplexy in adults with narcolepsy (October 2020) and both excessive daytime sleepiness and cataplexy in pediatric patients aged 6 years and older (2024 and February 2026, respectively) [9]. Beyond narcolepsy, the HAROSA trial program has demonstrated efficacy for residual excessive daytime sleepiness in obstructive sleep apnea, with statistically significant ESS reductions at both 20 mg and 40 mg doses [10, 11]. Exploratory clinical and preclinical investigations extend to epilepsy, Prader-Willi syndrome, Parkinson's disease-associated sleepiness, cognitive impairment, and obesity. Pharmacokinetics are characterized by high oral bioavailability (approximately 90%), rapid absorption with peak plasma concentrations at approximately 3 hours, plasma protein binding of 91 to 96%, and hepatic metabolism primarily via CYP2D6 and secondarily via CYP3A4, producing inactive metabolites conjugated with glycine or glucuronic acid [12]. The elimination half-life is 10 to 12 hours in most published pharmacokinetic analyses, though some reports note a range extending to 20 hours depending on the analytical methodology and population studied. CYP2D6 poor metabolizers exhibit approximately 2.4-fold increases in area under the curve, necessitating dose adjustment to a maximum of 17.8 mg daily in this population. The compound is well tolerated at approved doses of 8.9 to 35.6 mg daily; the principal adverse events are headache, insomnia, and nausea, with dose-dependent incidence [13]. QT interval prolongation is identified in the prescribing label, and the compound should be used with caution in patients with known QT prolongation or

concurrent QT-prolonging medications. This monograph reviews the chemistry, synthesis, receptor pharmacology, pharmacokinetics, preclinical pharmacology, clinical evidence base across all studied indications, sourcing and quality verification, reconstitution and handling, stack interactions, adverse-event signal, and a comparative assessment of five alternative wake-promoting or histamine-modulating agents against pitolisant on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Pitolisant.

Marketed names: Wakix (Bioprojet/Harmony Biosciences; European Union, United States, other jurisdictions), Ozawade (Bioprojet; European Union, approved for obstructive sleep apnea in some jurisdictions).

Development codes: BF2.649 (Bioprojet). The development code BF2.649 is the canonical identifier in the early pharmacology and clinical literature and is the designation under which the compound was characterized in the seminal Schwartz et al. (2011) review of H3 receptor pharmacology and clinical translation [1]. An earlier designation, tiprolisant, appears in some early literature but was superseded by the INN pitolisant.

Chemical Abstracts Service registry numbers: 362665-56-3 (free base), 903576-44-3 (hydrochloride salt). The hydrochloride salt is the formulated and marketed form; the free base is the synthetic precursor.

International Union of Pure and Applied Chemistry name: 1-{3-[3-(4-chlorophenyl)propoxy]propyl}piperidine. The compound is a non-imidazole piperidine derivative bearing a 4-chlorophenylpropoxy side chain connected through a propyl ether linker to the piperidine nitrogen.

1.2 Structural class and chemistry

Pitolisant belongs to the non-imidazole class of histamine H3 receptor ligands, a structural category developed to overcome the metabolic and selectivity limitations of the earlier imidazole-based H3 antagonists (thioperamide, ciproxifan, clobenpropit) that dominated the first generation of H3 pharmacology tools [1, 14]. The non-imidazole scaffold avoids CYP450 inhibition associated with the imidazole ring and provides improved oral bioavailability and CNS penetration.

Molecular formula: C₁₇H₂₆ClNO (free base); C₁₇H₂₇Cl₂NO (hydrochloride salt).

Molecular weight: 295.85 g/mol (free base); 332.31 g/mol (hydrochloride salt).

Exact mass: 295.1703 g/mol (free base, monoisotopic).

Physical properties: White to off-white crystalline powder. Soluble in water as the hydrochloride salt; soluble in methanol and ethanol; sparingly soluble in apolar organic solvents. The hydrochloride salt is hygroscopic and should be stored under dry conditions.

Stereochemistry: Pitolisant does not contain a stereocenter and is achiral. The compound is supplied and marketed as a single constitutional isomer without enantiomeric considerations. This simplifies synthesis, quality control, and regulatory characterization relative to chiral H3 ligands.

1.3 Synthesis

The published synthesis of pitolisant proceeds through well-characterized piperidine alkylation chemistry. The principal route described in the patent literature (Meier et al.) involves three stages: (a) N-alkylation of piperidine with 3-chloropropanol to produce the intermediate 3-(piperidin-1-yl)propan-1-ol; (b) O-alkylation of this intermediate with 3-(4-chlorophenyl)propyl methanesulfonate in the presence of sodium hydride and 15-crown-5 ether as phase-transfer catalyst to produce pitolisant free base; and (c) salt formation by treatment with gaseous hydrochloric acid to yield pitolisant hydrochloride [15]. An alternative industrial route disclosed in international patent WO2021023634A1 employs piperidine and 1-bromo-3-chloropropane as starting materials and is reported to be more economically efficient and scalable for manufacturing [16]. The compound is purified by recrystallization and characterized by nuclear magnetic resonance spectroscopy, mass spectrometry, and high-performance liquid chromatography. Typical synthetic yields for the final coupling step are 65 to 80 percent. The absence of stereochemistry simplifies the quality control burden relative to chiral drug substances.

2. Abstract

Pitolisant (BF2.649, Wakix) is a first-in-class histamine H3 receptor inverse agonist/antagonist developed by Bioprojet Societe Civile de Recherche and commercialized in the United States by Harmony Biosciences. The compound represents the clinical translation of three decades of histamine H3 receptor pharmacology initiated by the 1983 discovery of the H3 autoreceptor by Arrang, Garbarg, and Schwartz at INSERM in Paris [17]. By selectively blocking and inverting the constitutive activity of presynaptic H3 autoreceptors on tuberomamillary histaminergic neurons, pitolisant enhances endogenous histamine release throughout the brain, activating cortical arousal circuits and downstream monoaminergic and cholinergic wake-promoting systems without direct dopaminergic reinforcement in mesolimbic reward pathways [1, 3, 4].

The principal registered indication is the treatment of excessive daytime sleepiness in patients with narcolepsy type 1 (with cataplexy) and type 2 (without cataplexy), at oral doses of 8.9 to 35.6 mg once daily. The HARMONY clinical trial program established efficacy through three pivotal studies: HARMONY 1 (narcolepsy, excessive daytime sleepiness and cataplexy endpoints) [5, 6], HARMONY CTP (narcolepsy with cataplexy as primary endpoint) [7], and HARMONY III (12-month open-label safety and efficacy extension) [8]. The compound was non-inferior to modafinil on ESS reduction in a pooled meta-analytical comparison and demonstrated anti-cataplectic activity that modafinil does not possess [18]. The FDA approved the compound in August 2019 for excessive daytime sleepiness in adults with narcolepsy, expanded the indication to cataplexy in adults in October 2020, and subsequently approved pediatric indications for both excessive daytime sleepiness (2024) and cataplexy (February 2026) in patients aged 6 years and older [9].

A second clinical application, supported by the HAROSA trial program, is the treatment of residual excessive daytime sleepiness in patients with obstructive sleep apnea who remain symptomatic despite adherent continuous positive airway pressure therapy or who refuse or cannot tolerate CPAP [10, 11]. The compound is marketed as Ozawade in some European jurisdictions for this indication. A third exploratory application, supported by Phase 2 proof-of-concept data, is excessive daytime sleepiness in Prader-Willi syndrome, with a Phase 3 trial (TEMPO, NCT06366464) ongoing [19].

Preclinical and early clinical investigations extend the therapeutic scope to epilepsy (Phase 2 photosensitivity model data) [20], Parkinson's disease-associated sleepiness [21], cognitive impairment in schizophrenia and Alzheimer's disease [22, 23], and metabolic syndrome and obesity (preclinical mouse models demonstrating reduced body weight, improved glucose tolerance, and favorable lipid profiles) [24].

The compound is distinguished from other narcolepsy therapies by its non-controlled substance status, reflecting the absence of dopaminergic reinforcement and abuse liability in preclinical models [3, 4]. Pitolisant did not produce conditioned place preference, did not increase dopamine release in the nucleus accumbens, and did not produce behavioral locomotor sensitization on repeated dosing in rodent models, in contrast to amphetamine, modafinil, and solriamfetol [4]. This pharmacological profile supports a favorable benefit-risk assessment in a patient population that requires chronic, often lifelong, pharmacotherapy.

3. Discovery and Development History

3.1 Discovery of the histamine H3 receptor

The histamine H3 receptor was discovered in 1983 by Jean-Michel Arrang, Monique Garbarg, and Jean-Charles Schwartz at INSERM Unit 109 in Paris through a classical pharmacological approach: assessment of the inhibitory effect of histamine on its own release from depolarized rat cerebral cortex slices [17]. The receptor was characterized as a presynaptic autoreceptor that inhibited histamine synthesis and release through a negative feedback mechanism distinct from the previously characterized H1 and H2 receptors. This discovery established the conceptual foundation for a new class of central nervous system agents: compounds that could enhance brain histaminergic tone by blocking the autoreceptor brake.

3.2 First-generation H3 ligands

In 1987, the same INSERM-Bioprojet collaborative team developed the first highly selective and potent H3 receptor ligands: thioperamide (K_i approximately 4 nM), a potent antagonist, and (R)-alpha-methylhistamine, a potent agonist approximately 15-fold more potent than histamine itself [1, 14]. Both compounds were imidazole derivatives. Thioperamide became the canonical H3 antagonist research tool and demonstrated wake-promoting, procognitive, and anti-obesity effects in animal models, establishing the therapeutic rationale for H3 receptor blockade. However, imidazole-based H3 ligands suffered from poor oral bioavailability, hepatic CYP450 inhibition, and insufficient selectivity for clinical development.

3.3 H3 receptor cloning and constitutive activity

The cloning of the human H3 receptor gene in 1999 by Lovenberg et al. enabled recombinant expression screening and triggered H3 receptor drug discovery programs at multiple pharmaceutical companies [25]. A critical subsequent finding was the demonstration of high constitutive activity of the H3 receptor in native brain tissue, meaning that the receptor spontaneously adopted an active signaling conformation in the absence of agonist. This property distinguished inverse agonists (which suppress constitutive activity below basal levels) from neutral antago-

nists (which block agonist-induced activation but do not affect basal activity) and established inverse agonism as the preferred pharmacological mechanism for maximizing histaminergic tone enhancement [1, 2].

3.4 Development of pitolisant

Pitolisant (BF2.649) was selected from a series of non-imidazole piperidine derivatives synthesized at Bioprojet on the basis of sub-nanomolar H3 receptor binding affinity (K_i approximately 0.3 to 1.0 nM), potent inverse agonist activity (EC_{50} approximately 1.5 nM), high oral bioavailability (approximately 84% in preclinical species), adequate brain penetration, and an acceptable cardiovascular and toxicological safety profile [1, 2]. The non-imidazole scaffold was specifically designed to avoid the CYP450 inhibition and metabolic instability of the imidazole class. Pitolisant was advanced through preclinical safety studies in the early 2000s and entered clinical development at Bioprojet.

3.5 Clinical development and regulatory approvals

A 22-patient pilot study in narcolepsy demonstrated statistically significant reduction in Epworth Sleepiness Scale scores (from 17.2 to 12.4) [1]. Subsequent dose-finding and Phase 2 studies established the 10 to 40 mg dose range and confirmed wake-promoting activity across polysomnographic and subjective endpoints. The pivotal Phase 3 HARMONY 1 trial (2009 to 2010, 24 European centers, 95 narcolepsy patients) demonstrated statistically significant efficacy on ESS and cataplexy endpoints versus placebo [5, 6]. HARMONY CTP (2013 to 2015, 16 European centers, 105 narcolepsy patients with cataplexy) confirmed anti-cataplectic efficacy as the primary endpoint [7]. HARMONY III (open-label extension, 102 patients, 12 months) established long-term safety and sustained efficacy [8].

The European Medicines Agency granted marketing authorization for Wakix in March 2016 for the treatment of narcolepsy with or without cataplexy in adults, the first approval of a histamine H3 receptor modulator for any indication. The compound received orphan drug designation. The FDA approved Wakix in August 2019 for excessive daytime sleepiness in adults with narcolepsy, granting first-in-class, fast track, and breakthrough therapy designations [9]. The cataplexy indication in adults was approved in October 2020. Pediatric approvals for excessive daytime

sleepiness (2024) and cataplexy (February 2026) in patients aged 6 years and older extended the labeled population [9]. Harmony Biosciences holds the exclusive United States commercial license from Bioprojet.

4. Mechanism of Action

Pitolisant is a multi-target ligand whose principal molecular activity is inverse agonism at the histamine H3 receptor, with secondary binding at sigma-1, sigma-2, dopamine D3, and serotonin 5-HT2A receptors at higher concentrations. The H3 receptor inverse agonism and consequent histaminergic tone enhancement is the mechanism that underwrites the clinical wake-promoting and anti-cataplectic effects.

4.1 Histamine H3 receptor inverse agonism

The histamine H3 receptor (H3R) is a Gi/Go-coupled G protein-coupled receptor expressed predominantly on presynaptic terminals of histaminergic neurons in the tuberomammillary nucleus of the posterior hypothalamus, with additional expression on non-histaminergic neurons throughout the cortex, hippocampus, basal ganglia, and brainstem [1, 14]. The receptor functions as both an autoreceptor (inhibiting histamine synthesis and release from histaminergic neurons) and a heteroreceptor (modulating release of acetylcholine, norepinephrine, dopamine, serotonin, glutamate, and GABA from non-histaminergic terminals).

The H3 receptor exhibits high constitutive activity: in native brain tissue and in recombinant expression systems, the receptor spontaneously adopts an active Gi-coupled conformation that tonically inhibits histamine release even in the absence of agonist [1, 2]. Inverse agonists such as pitolisant not only block the effect of endogenous histamine at the autoreceptor but also suppress this constitutive activity below the basal level, producing a net enhancement of histamine release that exceeds what simple antagonism (competitive blockade without inverse agonism) can achieve.

Pitolisant binds the human H3 receptor with a K_i of approximately 0.3 to 1.0 nM (radioligand displacement assays) and functions as an inverse agonist with an EC_{50} of approximately 1.5 nM and intrinsic inverse agonist activity approximately 50% greater than the reference compound ciproxifan [1, 2]. In rat brain synaptosome preparations, pitolisant not only blocks the inhibitory effect of H3 agonists on his-

tamine release from depolarized terminals but also enhances histamine release above the basal (unstimulated) level, confirming functional inverse agonism in native tissue [1].

Positron emission tomography studies in healthy human subjects using the H3 receptor radioligand [11C]GSK189254 demonstrated that pitolisant at clinically relevant oral doses produces high occupancy (84 plus or minus 7%, mean plus or minus standard deviation) of brain H3 receptors, confirming target engagement at therapeutic concentrations [26].

4.2 Downstream neurotransmitter modulation

The enhancement of histaminergic tone by H3 receptor inverse agonism produces secondary activation of multiple wake-promoting neurotransmitter systems. Histaminergic neurons of the tuberomammillary nucleus project widely throughout the cortex and subcortex; increased histamine release activates postsynaptic H1 receptors on cortical neurons (promoting arousal and attention) and modulates cholinergic, noradrenergic, and dopaminergic projection systems through both direct histaminergic innervation and indirect circuit effects [1, 3, 14].

Critically, H3 heteroreceptor blockade on non-histaminergic terminals contributes to the increased release of acetylcholine in the cortex, norepinephrine in the locus coeruleus projection system, and dopamine in the prefrontal cortex [1, 3]. The dopaminergic modulation is anatomically selective: pitolisant increases dopamine release in the prefrontal cortex (supporting cognitive function) but does not increase dopamine release in the nucleus accumbens (the mesolimbic reward pathway target of psychostimulants) [3, 4]. This selectivity is the pharmacological basis for the low abuse potential and the non-controlled substance classification. In contrast, amphetamine, modafinil, and solriamfetol all produce measurable increases in nucleus accumbens dopamine in preclinical models [4].

4.3 Anti-cataplectic mechanism

The anti-cataplectic effect of pitolisant in narcolepsy type 1, demonstrated in HARMONY CTP with a 75% reduction in weekly cataplexy rate versus 38% for placebo [7], is attributed to histaminergic stabilization of the pontine circuits that regulate rapid eye movement sleep atonia. Narcolepsy type 1 is characterized by the loss of hypothalamic orexin (hypocretin) neurons, which normally activate the

tuberomamillary histaminergic system; exogenous enhancement of histamine release by pitolisant partially compensates for the orexin deficiency and stabilizes the inappropriate intrusion of REM atonia into wakefulness that manifests as cataplexy [14]. Additional contributions from noradrenergic and serotonergic pathway modulation, mediated through H3 heteroreceptor effects, may support the anti-cataplectic activity.

4.4 Secondary receptor activities

Pitolisant displays binding at several non-H3 targets at concentrations within one to two orders of magnitude of therapeutic plasma levels. Published binding affinity data include sigma-1 receptor agonism (K_i less than 10 nM), sigma-2 receptor antagonism (K_i approximately 52 nM), dopamine D3 receptor antagonism (K_i approximately 382 nM), and serotonin 5-HT_{2A} receptor antagonism (K_i approximately 544 nM) [27, 28]. The sigma-1 receptor affinity is notable because it approaches the H3 receptor affinity and may contribute to the *in vivo* pharmacological profile. Sigma-1 receptor agonism has been associated with neuroprotection, modulation of ion channel function, and endoplasmic reticulum stress response in preclinical models. The functional contribution of the sigma-1 receptor interaction to the clinical effects of pitolisant has not been definitively established but is a subject of active investigation [28].

The D3 and 5-HT_{2A} binding affinities are lower than therapeutic free plasma concentrations and are unlikely to contribute materially to the clinical pharmacology at approved doses.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Pitolisant is readily absorbed from the gastrointestinal tract after oral administration, with an oral bioavailability of approximately 90% [12, 29]. Peak plasma concentrations are achieved approximately 3 hours after oral dosing. Food does not meaningfully affect the rate or extent of absorption. The compound is administered as pitolisant hydrochloride in film-coated tablet form at strengths of 4.45 mg and 17.8 mg (expressed as pitolisant base equivalent).

5.2 Distribution

Plasma protein binding is high, at 91 to 96%, predominantly to albumin and alpha-1-acid glycoprotein [12, 29]. The compound crosses the blood-brain barrier; central nervous system penetration is confirmed by the high H3 receptor occupancy demonstrated in human PET studies [26]. Volume of distribution has not been precisely reported in the published literature for humans but is estimated to be moderate on the basis of the plasma protein binding, brain penetration, and lipophilicity of the compound.

5.3 Metabolism

Pitolisant is metabolized primarily in the liver by cytochrome P450 enzymes. The dominant metabolic pathway involves CYP2D6-mediated oxidation, with a secondary contribution from CYP3A4 [12, 29]. The resulting metabolites are pharmacologically inactive and are further conjugated with glycine or glucuronic acid before renal excretion.

CYP2D6 polymorphism affects pitolisant exposure. In CYP2D6 poor metabolizers (approximately 5 to 10% of European-ancestry populations), the area under the plasma concentration-time curve is increased approximately 2.4-fold relative to extensive metabolizers [12]. The prescribing label recommends a maximum dose of

17.8 mg daily in known CYP2D6 poor metabolizers. CYP2D6 ultrarapid metabolizers may exhibit reduced exposure, though formal dose adjustment recommendations for this phenotype have not been established.

CYP3A4 interactions are clinically relevant. Strong CYP3A4 inducers (rifampin, carbamazepine, phenytoin, St. John's wort) substantially reduce pitolisant exposure and may compromise efficacy. The prescribing label recommends dose adjustment when pitolisant is co-administered with strong CYP3A4 inducers [29].

5.4 Elimination

The elimination half-life of pitolisant is 10 to 12 hours in most published pharmacokinetic analyses, though some population pharmacokinetic reports describe a median half-life of approximately 20 hours with a range of 7.5 to 24.2 hours, reflecting inter-individual variability attributable in part to CYP2D6 polymorphism [12, 29]. The compound is eliminated predominantly as metabolites in the urine (approximately 63%) and feces (approximately 25%). Less than 2% of the administered dose is excreted unchanged in the urine.

5.5 Routes of administration

Pitolisant is administered exclusively by the oral route. The approved dosage forms are film-coated tablets containing pitolisant hydrochloride equivalent to 4.45 mg or 17.8 mg of pitolisant base. The recommended dosing regimen involves a titration from 8.9 mg once daily (two 4.45 mg tablets) in the first week to 17.8 mg once daily in the second week, with a maximum dose of 35.6 mg once daily achieved in the third week based on clinical response and tolerability [29]. The dose is taken once daily in the morning upon awakening to align with the wake-promoting pharmacology.

5.6 Special populations

Hepatic impairment: Moderate hepatic impairment (Child-Pugh B) increases pitolisant exposure approximately 2.4-fold. The maximum recommended dose in moderate hepatic impairment is 17.8 mg daily. The compound has not been studied in severe hepatic impairment (Child-Pugh C) and is not recommended in this population [29].

Renal impairment: Mild to moderate renal impairment does not require dose adjustment. In severe renal impairment (eGFR 15 to 29 mL/min/1.73 m²), the maximum recommended dose is 17.8 mg daily due to the potential for accumulation of metabolites [29].

Pediatric patients: Pharmacokinetics have been characterized in children and adolescents aged 6 years and older with narcolepsy. Weight-based dosing recommendations are provided in the prescribing label, with maximum doses of 17.8 mg daily for patients weighing less than 40 kg and 35.6 mg daily for patients weighing 40 kg or more [9].

Pregnancy and lactation: Pitolisant is not recommended during pregnancy. Animal reproductive studies have demonstrated adverse developmental effects (embryofetal toxicity, teratogenicity at supratherapeutic exposures). The compound is excreted in rat milk; human lactation data are limited, and use during breastfeeding is not recommended. The prescribing label includes a recommendation for effective contraception during treatment and for at least 21 days after discontinuation [29].

6. Preclinical Pharmacology

6.1 Wake-promoting activity

Pitolisant produces dose-dependent increases in wakefulness in rodent and feline electroencephalographic studies. In orexin-knockout mice (a genetic model of narcolepsy type 1), pitolisant increased wakefulness duration, reduced the number of direct transitions from wakefulness to rapid eye movement sleep (a correlate of cataplexy), and increased REM sleep latency [3, 14]. The wake-promoting effect is mediated through the histaminergic pathway: it is abolished in histidine decarboxylase knockout mice (which cannot synthesize histamine) and in H1 receptor knockout mice, confirming the requirement for intact histaminergic neurotransmission downstream of H3 receptor inverse agonism [1].

6.2 Absence of psychostimulant properties

The Krief et al. (2021) preclinical comparison of pitolisant with amphetamine, modafinil, and solriamfetol demonstrated that pitolisant does not produce behavioral locomotor sensitization on repeated administration, does not increase dopamine release in the nucleus accumbens (measured by *in vivo* microdialysis), and does not produce conditioned place preference at any tested dose [4]. In contrast, amphetamine produced robust dopaminergic activation in the accumbens, locomotor sensitization, and conditioned place preference; modafinil produced moderate dopaminergic effects; and solriamfetol produced intermediate effects. These findings support the classification of pitolisant as a eugeroic (wake-promoting agent) devoid of psychostimulant properties and the non-controlled substance regulatory status.

6.3 Procognitive activity

Pitolisant enhanced performance in rodent object recognition, passive avoidance, and social recognition memory tasks, consistent with the procognitive effects of histaminergic tone enhancement in the cortex and hippocampus [1, 22]. The mechanism involves both direct H1 receptor-mediated cortical arousal and H3 heteroreceptor-mediated enhancement of acetylcholine and dopamine release in the pre-

frontal cortex. Recent preclinical work has demonstrated that pitolisant alleviates brain network dysfunction and cognitive deficits in a mouse model of Alzheimer's disease, with improvements in hippocampal connectivity and spatial memory performance [23].

6.4 Anti-obesity and metabolic effects

The Inocente et al. (2018) study demonstrated that pitolisant reduces body weight in diet-induced obese mice, with significant reductions in plasma triglyceride levels, improved glucose tolerance, and favorable lipid profile changes compared to control obese animals [24]. The mechanism is attributed to histaminergic activation of hypothalamic satiety circuits and to peripheral metabolic effects of enhanced histamine signaling. The anti-obesity effect is consistent with the known role of brain histamine in energy homeostasis regulation and with observations that H3 receptor knockout mice are resistant to diet-induced obesity.

6.5 Anticonvulsant activity

Preclinical studies in multiple rodent seizure models have demonstrated anticonvulsant activity of H3 receptor antagonists and inverse agonists, including pitolisant [20]. The mechanism involves histaminergic enhancement of cortical inhibitory tone and modulation of glutamatergic and GABAergic transmission through H3 heteroreceptor effects. These preclinical findings provided the rationale for the Phase 2 clinical evaluation in photosensitive epilepsy.

6.6 Abuse potential assessment

The comprehensive abuse liability assessment conducted for regulatory submission included self-administration studies in non-human primates, conditioned place preference studies in rodents, drug discrimination studies, and physical dependence assessments [3, 4]. Pitolisant did not maintain self-administration above vehicle rates, did not substitute for amphetamine or cocaine in drug discrimination paradigms, did not produce conditioned place preference, and did not produce physical dependence or withdrawal signs on abrupt discontinuation. These findings, combined with the absence of nucleus accumbens dopamine release, supported the non-controlled substance determination by both the FDA and the EMA.

7. Clinical Evidence Base

7.1 Narcolepsy: HARMONY 1

The HARMONY 1 trial was a randomized, double-blind, placebo-controlled, parallel-group study conducted at 24 centers in Europe between May 2009 and June 2010 [5, 6]. Ninety-five patients with narcolepsy (type 1 and type 2) were randomized to pitolisant (individualized dosing, 10 to 40 mg once daily), modafinil (100 to 400 mg daily, active comparator), or placebo for 8 weeks. The primary endpoint was change in Epworth Sleepiness Scale score from baseline.

Pitolisant produced a statistically significant reduction in ESS score versus placebo (mean difference approximately 3 points; Cohen's d 0.61; p less than 0.05) [5, 6]. ESS responders (final score of 10 or less) were 45.2% for pitolisant versus 13.3% for placebo (p less than 0.001). Pitolisant was non-inferior to modafinil on the ESS primary endpoint in pooled meta-analytical comparison [18]. On secondary endpoints, pitolisant produced a 62% mean reduction in weekly cataplexy rate versus 8% for placebo (p equals 0.034), establishing anti-cataplectic activity that had not been demonstrated for modafinil [5, 6].

7.2 Narcolepsy: HARMONY CTP

The HARMONY CTP (Cataplexy Treatment in Patients with narcolepsy) trial was a randomized, double-blind, placebo-controlled study conducted at 16 European centers between April 2013 and January 2015 [7]. One hundred and five patients with narcolepsy type 1 and frequent cataplexy (at least 3 episodes per week) were randomized to pitolisant (individualized dosing, 4.5 to 36 mg once daily) or placebo for 7 weeks. The primary endpoint was change in weekly rate of cataplexy attacks.

Pitolisant produced a 75% mean reduction in weekly cataplexy rate versus 38% for placebo (p less than 0.0001; Cohen's d 0.86) [7]. ESS scores improved significantly in the pitolisant group (mean reduction approximately 3 points versus placebo). The study confirmed the dual efficacy of pitolisant against both excessive daytime sleepiness and cataplexy, a combination that is shared among approved narcolepsy therapies only by sodium oxybate.

7.3 Narcolepsy: HARMONY III

The HARMONY III open-label extension study enrolled 102 narcolepsy patients (including those completing HARMONY 1 and newly recruited patients) for 12 months of continuous pitolisant treatment at individualized doses of 4.5 to 36 mg once daily [8]. Sustained efficacy was demonstrated on ESS scores and cataplexy rate reduction throughout the 12-month treatment period. The safety profile was consistent with the controlled trials, with no new safety signals identified and no evidence of tolerance development or loss of efficacy over time.

7.4 Obstructive sleep apnea: HAROSA program

The HAROSA trial program evaluated pitolisant for residual excessive daytime sleepiness in patients with obstructive sleep apnea. HAROSA I enrolled patients adherent to CPAP therapy; HAROSA II enrolled patients refusing or not tolerating CPAP [10, 11]. In pooled individual patient meta-analysis of 423 patients, pitolisant at 20 mg and 40 mg produced statistically significant reductions in ESS score versus placebo (treatment effects of negative 3.20 and negative 3.57 points, respectively) and improved objective sleepiness measures (OSLER test) [10, 11]. HAROSA III confirmed efficacy of the 40 mg dose irrespective of CPAP use [11]. Long-term follow-up data demonstrated sustained efficacy and a favorable safety profile over 12 months of treatment.

7.5 Prader-Willi syndrome

A Phase 2 randomized, double-blind, placebo-controlled proof-of-concept study enrolled 65 patients aged 6 to 65 years with Prader-Willi syndrome and excessive daytime sleepiness [19]. Patients receiving pitolisant demonstrated clinically meaningful improvements on the ESS-CHAD Parent/Caregiver Version (3.7 to 5.5 point improvements), with the largest effect observed in children aged 6 to less than 12 years (least-squares mean difference versus placebo of negative 3.5 points for the higher-dose group). Secondary endpoints showed improvements in irritability (Aberrant Behavior Checklist-Community) and hyperphagia (Hyperphagia Questionnaire for Clinical Trials). A Phase 3 confirmatory trial (TEMPO, NCT06366464) is ongoing.

7.6 Epilepsy

A Phase 2 study evaluated pitolisant in 12 patients with photosensitive epilepsy using the human photosensitivity model [20]. Single doses of 20 to 60 mg reduced the photoparoxysmal response on electroencephalography in a dose-dependent manner. The compound has not been advanced to Phase 3 for epilepsy indications.

7.7 Parkinson's disease

A double-blind, dose-ranging Phase 2 trial in 107 patients with Parkinson's disease and excessive daytime sleepiness demonstrated that pitolisant at a minimum efficacious dose of 20 mg produced significant improvement in objective sleepiness measures with a monotonic dose-response relationship [21]. Motor symptomatology was not affected. The compound has not been advanced to Phase 3 for Parkinson's disease.

7.8 Cognitive and psychiatric applications

Preclinical and early clinical data support investigation of pitolisant in cognitive impairment associated with schizophrenia and neurodegenerative diseases [22, 23]. The mechanism (enhanced cortical acetylcholine and dopamine release through H3 heteroreceptor blockade) is complementary to the cholinesterase inhibitor approach used in Alzheimer's disease. Clinical data in these indications are limited to exploratory Phase 2 studies and case series; registration-quality evidence is not available.

8. Sourcing and Quality Verification

Pharmaceutical-grade pitolisant (Wakix brand, Harmony Biosciences in the United States; Bioprojet in the European Union) is the highest quality source for clinical and clinical-research applications. The pharmaceutical-grade material is supplied as film-coated tablets containing pitolisant hydrochloride equivalent to 4.45 mg or 17.8 mg of pitolisant base. The compound is available by prescription in the United States and in the European Union.

Research-grade pitolisant hydrochloride is supplied by multiple chemical and pharmaceutical research suppliers (Tocris, Sigma-Aldrich/Merck, Cayman Chemical, MedChemExpress, Selleckchem, and others) at greater than 98% purity by HPLC. Supply is available in milligram to gram quantities as the hydrochloride salt. Pricing is moderate to high for the research-grade material, reflecting the relatively specialized market.

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

- High-performance liquid chromatography area-percent purity, ideally greater than 98%
- Mass spectrometry confirmation of molecular weight (296.17 plus or minus 0.01 for the protonated free base $[M+H]^+$, or 332.13 for the hydrochloride)
- Nuclear magnetic resonance spectroscopy (1H and ^{13}C) for structural confirmation
- Karl Fischer or loss-on-drying analysis for residual water content
- Residual solvent analysis by gas chromatography

Third-party analytical laboratories provide independent confirmation of vendor certificates of analysis. The research-grade pitolisant market is established, and counterfeit material is uncommon, but lot-to-lot variability in purity and residual solvent content is observed. On-receipt analytical confirmation is appropriate for dose-response and mechanistic investigations.

9. Reconstitution and Handling

Pitolisant hydrochloride is soluble in water at room temperature. For in vitro research applications, the compound is supplied as a crystalline powder and is reconstituted in water, phosphate-buffered saline, or dimethyl sulfoxide to prepare stock solutions. Typical stock concentrations are 10 to 50 mM in dimethyl sulfoxide or 1 to 10 mg/mL in aqueous solution.

For in vivo research, pitolisant is typically dissolved in saline or in acidified water (pH 4 to 5 with hydrochloric acid or citrate buffer) for oral gavage or intraperitoneal injection. The compound is stable in aqueous solution at pH 4 to 7 at room temperature for at least 24 hours and at refrigerated conditions (2 to 8 degrees Celsius) for at least 7 days.

Storage of the solid compound should be at room temperature (15 to 25 degrees Celsius) in a dry, light-protected environment. The hydrochloride salt is modestly hygroscopic; exposure to high humidity should be minimized. Long-term storage at negative 20 degrees Celsius is appropriate for research-grade bulk material.

Aliquoting of stock solutions for single-use is recommended to minimize freeze-thaw cycles. Stability data indicate that aqueous and DMSO stock solutions tolerate at least 3 freeze-thaw cycles without measurable potency loss, though single-use aliquoting remains best practice.

For clinical use, the film-coated tablets should be stored at controlled room temperature (20 to 25 degrees Celsius, with excursions permitted between 15 and 30 degrees Celsius) in the original blister packaging until use. No reconstitution is required for oral administration.

10. Stack Interaction Considerations

Pitolisant interacts with several drug classes through its CYP-mediated metabolism and through its pharmacodynamic effects on histaminergic and monoaminergic systems. Investigators and clinicians should consider:

CYP2D6 inhibitors: Strong CYP2D6 inhibitors (paroxetine, fluoxetine, bupropion, quinidine, terbinafine) increase pitolisant exposure by reducing CYP2D6-mediated metabolism. The combination requires monitoring for increased adverse events but does not require automatic dose reduction unless the patient is also a CYP2D6 intermediate or poor metabolizer [29].

CYP3A4 inducers: Strong CYP3A4 inducers (rifampin, carbamazepine, phenytoin, phenobarbital, St. John's wort) substantially reduce pitolisant exposure and may compromise clinical efficacy. The prescribing label recommends increasing the pitolisant dose when co-administered with strong CYP3A4 inducers [29].

CYP3A4 inhibitors: Moderate and strong CYP3A4 inhibitors (ketoconazole, itraconazole, clarithromycin, grapefruit juice) modestly increase pitolisant exposure. Dose adjustment may be appropriate in patients concurrently taking strong CYP3A4 inhibitors, particularly in combination with CYP2D6 inhibition.

CYP2B6 substrates: Pitolisant is a weak inducer of CYP2B6 and may reduce the exposure of CYP2B6 substrates. The prescribing label includes a specific warning regarding the potential for reduced efficacy of hormonal contraceptives (which are partially metabolized by CYP2B6 and CYP3A4) during pitolisant treatment [29].

QT-prolonging agents: Pitolisant prolongs the QT interval at supratherapeutic concentrations. Combination with other QT-prolonging agents (sotalol, amiodarone, erythromycin, haloperidol, methadone, certain fluoroquinolones) increases the arrhythmia risk and should be approached with caution. The risk is greater in patients with elevated pitolisant concentrations (CYP2D6 poor metabolizers, hepatic impairment, concurrent CYP inhibition) [29].

H1 receptor antagonists: First-generation antihistamines (diphenhydramine, chlorpheniramine, hydroxyzine) antagonize the H1 receptor through which pitolisant exerts its downstream wake-promoting effect. Concurrent use may atten-

uate the clinical efficacy of pitolisant and is generally not recommended. Second-generation antihistamines with limited CNS penetration (cetirizine, loratadine, fexofenadine) are less likely to interfere.

Other wake-promoting agents: Combination with modafinil, armodafinil, solriamfetol, or amphetamine-based stimulants produces additive or overlapping wake-promoting effects through distinct mechanisms. The combination has not been formally studied in controlled trials but is used in clinical practice for refractory narcolepsy. Additive cardiovascular effects (tachycardia, hypertension) should be monitored.

Sodium oxybate: Combination with sodium oxybate is used clinically for narcolepsy patients requiring both anti-cataplectic and wake-promoting therapy. No direct pharmacokinetic interaction has been characterized. The combination is pharmacodynamically complementary (nocturnal sodium oxybate consolidating sleep, daytime pitolisant promoting wakefulness).

Opioids: No direct pharmacokinetic interaction is characterized. Pitolisant does not produce additive respiratory depression with opioids, a distinction from some other CNS-active narcolepsy therapies.

11. Adverse Events and Safety

11.1 Common adverse events

The principal adverse events at approved doses (8.9 to 35.6 mg daily) in clinical trials are [13, 29]:

- Insomnia (6 to 8.4%, dose-dependent; reflects the pharmacological wake-promoting effect and is managed by morning dosing and dose adjustment)
- Headache (5 to 7.7%)
- Nausea (4.8 to 6%)
- Anxiety (2.1 to 5%)
- Irritability (1.8%)
- Dizziness (1.4%)
- Depression (1.3%)
- Tremor (1.2%)
- Vertigo (1.0%)
- Vomiting (1%)
- Diarrhea (1%)

Adverse event incidence is dose-dependent. In a pooled analysis of over 1,800 subjects, incidence rates were 11.1% at 4.5 mg daily, 20.3% at 9 mg daily, 32.5% at 18 mg daily, and 36.4% at 36 mg daily [13].

11.2 QT interval prolongation

The prescribing label identifies QT interval prolongation as a risk, based on a thorough QT study demonstrating concentration-dependent QTc prolongation at supratherapeutic doses [29]. Patients with known QT prolongation, concurrent QT-prolonging medications, electrolyte abnormalities (hypokalemia, hypomagnesemia), or hepatic or renal impairment that may elevate pitolisant concentrations are at increased risk. ECG monitoring is recommended in at-risk populations.

11.3 Neuropsychiatric effects

The prescribing label includes warnings regarding potential for depression, suicidal ideation, and hallucinations, based on isolated reports in clinical trials and postmarketing surveillance [29]. The sigma-1 receptor agonist activity of pitolisant is a theoretical contributor to neuropsychiatric effects, though a causal relationship has not been established. Patients with pre-existing psychiatric conditions should be monitored during treatment initiation and dose changes.

11.4 Weight effects

Abnormal weight loss has been reported in clinical trials, consistent with the anti-obesity pharmacology observed in preclinical models [24, 29]. Weight should be monitored during treatment, particularly in pediatric patients and in patients with low body mass index.

11.5 Reproductive toxicity

Animal studies demonstrated embryofetal toxicity and teratogenicity at supratherapeutic exposures. Spontaneous abortion has been reported in postmarketing surveillance. The compound is not recommended during pregnancy, and effective contraception is recommended during treatment and for at least 21 days after the last dose [29].

11.6 CYP2D6 poor metabolizer safety

CYP2D6 poor metabolizers experience approximately 2.4-fold higher systemic exposure, increasing the likelihood and severity of dose-dependent adverse events. The maximum recommended dose in known poor metabolizers is 17.8 mg daily [29].

11.7 Long-term safety

The HARMONY III 12-month open-label study and subsequent long-term extension data demonstrated sustained tolerability without evidence of tolerance development, loss of efficacy, rebound hypersomnia on discontinuation, or new safety signals emerging with chronic use [8]. No evidence of physical dependence or withdrawal symptoms has been reported.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five alternative wake-promoting or histamine-modulating agents against pitolisant, 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 to represent the principal pharmacological alternatives for the narcolepsy and excessive daytime sleepiness indications and include both established and investigational agents.

12.1 Modafinil (Provigil)

Mechanism: Wake-promoting agent with complex, incompletely characterized mechanism involving dopamine transporter inhibition, increased extracellular dopamine, norepinephrine, histamine, and orexin levels. Weak dopamine transporter inhibitor with downstream effects on multiple arousal systems [30].

Development trajectory: Developed by Lafon Laboratories (France), approved by the FDA in 1998 for narcolepsy, subsequently approved for obstructive sleep apnea and shift work disorder. Classified as Schedule IV controlled substance in the United States. Now extensively generic.

Novelty: Low. The compound has been available for over 25 years and the mechanism is well characterized.

Effect size: HARMONY 1 included modafinil as an active comparator. Pitolisant was non-inferior to modafinil on ESS reduction [5, 18]. Modafinil produces ESS reductions of approximately 4 to 5 points versus placebo in registration trials. Modafinil does not produce significant anti-cataplectic activity, a meaningful limitation in narcolepsy type 1.

Promising potential: Moderate as a sustained standard of care. The compound remains first-line for excessive daytime sleepiness in narcolepsy and obstructive sleep apnea in most treatment guidelines. However, it does not address cataplexy and carries controlled-substance restrictions.

Side-effect profile: Headache (34%), nausea (11%), nervousness (7%), rhinitis (7%), and insomnia (5%) are the most common adverse events. Serious adverse events include Stevens-Johnson syndrome and toxic epidermal necrolysis (rare but severe). The compound carries a controlled-substance classification (Schedule IV) reflecting abuse potential, though the abuse liability is lower than amphetamine-based agents.

Overall validation: High. Extensive clinical evidence base spanning decades of use, multiple large randomized controlled trials, and well-characterized long-term safety.

Comparison to pitolisant: Modafinil and pitolisant produce comparable reductions in excessive daytime sleepiness. Pitolisant has the advantage of anti-cataplectic activity, non-controlled substance status, and a mechanistically distinct (histaminergic rather than dopaminergic) wake-promoting pathway. Modafinil has the advantages of extensive clinical experience, low cost (generic), broad guideline positioning, and additional approved indications (shift work disorder).

12.2 Solriamfetol (Sunosi)

Mechanism: Dual dopamine and norepinephrine reuptake inhibitor. Increases synaptic concentrations of both monoamines through transporter blockade without direct release activity (distinguishing it from amphetamine) [31].

Development trajectory: Developed by Jazz Pharmaceuticals (originally Aerial BioPharma/SK Biopharmaceuticals). Approved by the FDA in March 2019 for excessive daytime sleepiness in narcolepsy and obstructive sleep apnea. Classified as Schedule IV controlled substance.

Novelty: Moderate. The dual reuptake inhibitor mechanism in the context of wake promotion is a relatively novel positioning, though monoamine reuptake inhibition is a well-established pharmacological strategy.

Effect size: Solriamfetol produces dose-dependent ESS reductions of approximately 3 to 6 points versus placebo at approved doses (75 to 150 mg for narcolepsy, 37.5 to 150 mg for OSA). Effect sizes are broadly comparable to modafinil and pitolisant for excessive daytime sleepiness. Solriamfetol does not demonstrate significant anti-cataplectic activity [31].

Promising potential: Moderate to high. The compound is gaining clinical adoption for narcolepsy and OSA. However, it lacks anti-cataplectic activity and carries controlled-substance restrictions.

Side-effect profile: Headache (8 to 16%), nausea (6 to 9%), decreased appetite (6 to 9%), insomnia (4 to 6%), and anxiety (3 to 6%). Cardiovascular effects include dose-dependent increases in blood pressure and heart rate, a concern in the OSA population with high cardiovascular comorbidity. The compound increases nucleus accumbens dopamine in preclinical models, supporting the controlled-substance classification [4, 31].

Overall validation: Moderate to high. Multiple large randomized controlled trials in narcolepsy and OSA, FDA-approved for both indications, growing real-world evidence.

Comparison to pitolisant: Solriamfetol may produce slightly larger ESS reductions at higher doses but lacks anti-cataplectic activity. Pitolisant has the advantages of anti-cataplectic efficacy, non-controlled substance status, and absence of cardiovascular stimulant effects. Solriamfetol may be preferred in patients who do not respond adequately to pitolisant for sleepiness and who do not require anti-cataplectic therapy. Cost-effectiveness analyses have found solriamfetol to be less expensive than pitolisant with marginally less efficacy for sleepiness.

12.3 Sodium Oxybate (Xyrem, Xywav)

Mechanism: Central nervous system depressant acting through GABA-B receptor agonism and GHB receptor agonism. Consolidates nocturnal sleep architecture and reduces cataplexy through poorly characterized downstream mechanisms involving enhanced slow-wave sleep and monoaminergic modulation [32].

Development trajectory: Developed by Jazz Pharmaceuticals (Orphan Medical). FDA-approved in 2002 for cataplexy in narcolepsy, subsequently approved for excessive daytime sleepiness in narcolepsy. Classified as Schedule III controlled substance with a Risk Evaluation and Mitigation Strategy (REMS) program. Xywav (lower-sodium formulation) approved in 2020.

Novelty: Low. The compound has been available for over 20 years. The mechanism remains unique among narcolepsy therapies.

Effect size: Sodium oxybate produces the largest effect sizes among approved narcolepsy therapies for both cataplexy (greater than 80% reduction at therapeutic doses) and excessive daytime sleepiness (ESS reductions of 5 to 7 points versus placebo). It is the only approved narcolepsy therapy that addresses both symptoms, nocturnal sleep disruption, and sleep paralysis/hallucinations [32].

Promising potential: High as the most comprehensive single-agent narcolepsy therapy. Limitations include the REMS program, twice-nightly dosing, Schedule III controlled-substance classification, and the burden of the titration regimen.

Side-effect profile: Nausea (20 to 40%), dizziness (15 to 20%), headache (15 to 25%), vomiting (8 to 15%), somnolence, enuresis, and tremor. Serious adverse events include respiratory depression (especially in combination with other CNS depressants), abuse and misuse potential, and confusion/anxiety. The REMS program reflects the controlled-substance status and the risk of misuse. High sodium content in the original Xyrem formulation raised cardiovascular concerns in patients with hypertension; the lower-sodium Xywav partially addresses this.

Overall validation: High. The most comprehensively validated narcolepsy therapy with efficacy across the full symptom spectrum.

Comparison to pitolisant: Sodium oxybate is more efficacious for cataplexy and produces larger effect sizes for sleepiness than pitolisant, but carries substantially greater regulatory burden (REMS, Schedule III), dosing complexity (twice-nightly administration), and adverse-event burden. Pitolisant offers a more favorable tolerability profile, once-daily morning dosing, non-controlled substance status, and an acceptable (though smaller) anti-cataplectic effect. The two compounds are pharmacodynamically complementary and are used in combination in clinical practice (pitolisant for daytime wakefulness, sodium oxybate for nocturnal sleep consolidation and cataplexy).

12.4 Thioperamide

Mechanism: First-generation imidazole-based histamine H3 receptor antagonist with K_i approximately 4 nM [14]. The canonical H3 receptor research tool compound.

Development trajectory: Thioperamide was synthesized in 1987 by the INSERM-Bioprojet collaborative team and became the standard H3 antagonist for basic research [14, 17]. The compound was not advanced to clinical development due to

hepatotoxicity, poor oral bioavailability, and insufficient selectivity (substantial off-target binding at H4 receptors and at other sites). It remains exclusively a research compound.

Novelty: Low. The compound is the oldest and most extensively characterized H3 antagonist.

Effect size: Robust wake-promoting, procognitive, and anti-obesity effects in rodent models. No human clinical data exist.

Promising potential: None as a clinical candidate. Persistent value as a reference compound for fundamental H3 receptor pharmacology research.

Side-effect profile: Hepatotoxicity in animal studies precluded clinical development. Poor selectivity profile with significant H4 receptor cross-reactivity. The imidazole ring structure inhibits hepatic CYP450 enzymes [14].

Overall validation: High as a research tool; no clinical validation.

Comparison to pitolisant: Thioperamide is the historical predecessor of pitolisant in the H3 receptor pharmacology lineage. Pitolisant was specifically designed to overcome the limitations of thioperamide and the imidazole class: improved oral bioavailability, absence of CYP450 inhibition, improved selectivity, and an acceptable safety profile for clinical use. Pitolisant is the direct clinical translation of the H3 receptor pharmacology concept that thioperamide established.

12.5 Ciproxifan

Mechanism: Imidazole-based histamine H3 receptor inverse agonist with potent intrinsic inverse agonist activity [1, 14]. Served as the reference inverse agonist in the pharmacological characterization of pitolisant.

Development trajectory: Developed at Bioprojet/INSERM as a research tool and pharmacological reference compound. Not advanced to clinical development due to the same imidazole-class limitations (CYP450 inhibition, limited oral bioavailability, off-target binding). Research-grade ciproxifan is widely available from chemical suppliers.

Novelty: Low. The compound is a well-characterized reference inverse agonist.

Effect size: Potent wake-promoting, procognitive, and anti-obesity effects in rodent models. Pitolisant was specifically compared to ciproxifan in the Schwartz et al. (2011) characterization, with pitolisant showing approximately 50% greater intrinsic inverse agonist activity [1].

Promising potential: None as a clinical candidate. Persistent value as a reference inverse agonist for H3 receptor pharmacology.

Side-effect profile: Imidazole-class limitations (CYP450 inhibition). No human safety data.

Overall validation: Moderate as a research tool. No clinical validation.

Comparison to pitolisant: Ciproxifan served as the pharmacological benchmark for pitolisant development. Pitolisant exceeds ciproxifan in intrinsic inverse agonist activity, has substantially improved pharmacokinetic properties, and has achieved clinical registration. Ciproxifan remains a useful reference compound for in vitro H3 receptor pharmacology but is not a clinical alternative.

12.6 Comparator summary

The five comparators occupy distinct positions in the narcolepsy and wake-promotion therapeutic landscape. **Modafinil** represents the established first-line standard with extensive clinical experience but limited efficacy scope (no anti-cataplectic activity) and controlled-substance classification. **Solriamfetol** is a newer dopaminergic/noradrenergic agent with comparable sleepiness efficacy but no anti-cataplectic activity, cardiovascular stimulant effects, and controlled-substance status. **Sodium oxybate** is the most comprehensively efficacious narcolepsy therapy but carries the greatest regulatory and tolerability burdens. **Thiopramide** and **ciproxifan** are the historical and pharmacological predecessors of pitolisant, respectively, with robust preclinical profiles but no clinical pathway.

Pitolisant occupies a unique position as the only approved histamine H3 receptor modulator, the only non-controlled wake-promoting agent with anti-cataplectic activity, and the most mechanistically differentiated alternative to dopaminergic and GABAergic narcolepsy therapies. Its clinical evidence base is smaller than that of modafinil or sodium oxybate but is growing with the HAROSA, Prader-Willi, and pediatric programs. The non-controlled substance status, the once-daily oral dosing, the favorable cardiovascular safety profile, and the dual efficacy against sleepi-

ness and cataplexy position pitolisant as a clinically distinctive agent in a therapeutic area where drug scheduling, abuse potential, and dosing complexity are material considerations for patients and prescribers.

The principal practical question for pitolisant's positioning is whether the moderate effect sizes (Cohen's d 0.6 to 0.9, broadly comparable to modafinil) and the novel histaminergic mechanism are sufficient to support broader first-line adoption, or whether the compound will remain positioned primarily for patients who are inadequately controlled on, intolerant of, or have contraindications to traditional stimulants and sodium oxybate. The non-controlled substance status is a meaningful differentiator that may influence prescribing patterns as regulatory scrutiny of controlled-substance prescribing in narcolepsy increases.

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