

## RESEARCH MONOGRAPH . COMPOUND PROFILE

# Solriamfetol

*A phenylalanine-derived dual dopamine-norepinephrine reuptake inhibitor developed by SK Biopharmaceuticals and commercialized by Jazz Pharmaceuticals as the first DNRI approved for the treatment of excessive daytime sleepiness associated with narcolepsy and obstructive sleep apnea.*

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| COMPOUND CLASS | Selective dopamine and norepinephrine reuptake inhibitor (DNRI) with trace amine-associated receptor 1 (TAAR1) agonist activity |

## ABSTRACT

Solriamfetol (JZP-110, SKL-N05, ADX-N05) is a selective dopamine and norepinephrine reuptake inhibitor (DNRI) approved in the United States (March 2019) and the European Union (January 2020) for the treatment of excessive daytime sleepiness (EDS) in adults with narcolepsy or obstructive sleep apnea (OSA). Chemically derived from the amino acid D-phenylalanine, solriamfetol is the (R)-enantiomer of 2-amino-3-phenylpropyl carbamate and is supplied as the hydrochloride salt for oral administration. The compound inhibits the reuptake of dopamine (IC<sub>50</sub> approximately 2.9 micromolar) and norepinephrine (IC<sub>50</sub> approximately 4.4 micromolar) at their respective plasma membrane transporters (DAT and NET) with minimal activity at the serotonin transporter. In addition, solriamfetol acts as an agonist at the human trace amine-associated receptor 1 (TAAR1) with an EC<sub>50</sub> of approximately 10 to 16 micromolar, a concentration range overlapping its DAT and NET inhibitory potencies and achieved at clinically relevant plasma levels. Critically, the compound does not promote monoamine release, distinguishing it mechanistically from amphetamine and its analogs and supporting its classification as a reuptake inhibitor rather than a releasing agent. The clinical development program comprised five pivotal trials (TONES 1 through TONES 5). The Phase 3 TONES 2 trial in 231 narcolepsy patients demonstrated that solriamfetol at 150 mg and 300 mg once daily produced statistically significant improvements in the Maintenance of Wakefulness Test (MWT) mean sleep latency (increases of 9.8 and 12.3 minutes, respectively, versus 2.1 minutes for placebo at 12 weeks) and in the Epworth Sleepiness Scale

(ESS). The Phase 3 TONES 3 trial in 459 OSA patients demonstrated similar dose-dependent improvements at 37.5, 75, 150, and 300 mg doses. The long-term TONES 5 open-label extension in 643 participants confirmed maintenance of efficacy and tolerability over 52 weeks. A randomized withdrawal phase within TONES 5 demonstrated that participants switched to placebo experienced a return of sleepiness (ESS worsening of 5.3 points versus 1.6 points for those continuing solriamfetol), confirming sustained pharmacological activity rather than natural remission. Pharmacokinetics are notable for high oral bioavailability (approximately 95 percent), minimal hepatic metabolism (less than 1 percent of dose recovered as the sole inactive metabolite N-acetyl solriamfetol), and predominant renal elimination of unchanged drug through active tubular secretion. The elimination half-life is approximately 7.1 hours in subjects with normal renal function. Because metabolism is negligible, solriamfetol carries essentially no cytochrome P450 drug interaction liability. However, renal impairment substantially prolongs elimination (half-life increased approximately 1.2-, 1.9-, and 3.9-fold in mild, moderate, and severe renal impairment, respectively), requiring dose adjustment in moderate and severe renal impairment and avoidance in end-stage renal disease. The principal adverse events are headache, nausea, decreased appetite, insomnia, and anxiety. Solriamfetol produces small, dose-dependent increases in systolic blood pressure (0.5 to 2.5 mmHg), diastolic blood pressure, and heart rate (0.7 to 2.9 beats per minute), consistent with its noradrenergic mechanism. Concurrent use with monoamine oxidase inhibitors is contraindicated. The compound is designated Schedule IV in the United States, reflecting low but measurable abuse potential at supratherapeutic doses. This monograph reviews the chemistry,

synthesis, and stereochemistry of solriamfetol; the dual-transporter and TAAR1 pharmacology; the comprehensive pharmacokinetic profile; the clinical evidence base across narcolepsy and OSA indications; the sourcing and quality verification considerations for research applications; reconstitution and handling; stack-interaction implications; adverse-event signal; and a comparative assessment of five wake-promoting agents against solriamfetol on five competency standards.

# 1. Compound Identification

## 1.1 Names, synonyms, and registry identifiers

**International Nonproprietary Name:** Solriamfetol.

**Marketed name:** Sunosi (Jazz Pharmaceuticals; United States, European Union member states, and other jurisdictions). The product was subsequently acquired by Axsome Therapeutics from Jazz Pharmaceuticals in 2022 for United States commercialization.

**Development codes:** JZP-110 (Jazz Pharmaceuticals), ADX-N05 (Aerial BioPharma), ARL-N05, SKL-N05 (SK Biopharmaceuticals). The compound appears under these codes in the clinical trial registries and the earlier pharmacology literature.

**Chemical Abstracts Service registry numbers:** 178429-62-4 (free base), 178429-65-7 (hydrochloride salt). The hydrochloride salt is the pharmaceutical form.

**International Union of Pure and Applied Chemistry name:** [(2R)-2-amino-3-phenylpropyl] carbamate. The compound is the carbamate ester of (R)-2-amino-3-phenylpropan-1-ol, a derivative of the natural amino acid D-phenylalanine.

## 1.2 Structural class and chemistry

Solriamfetol is a phenylpropylamine carbamate. Structurally, it belongs to a small class of amino acid-derived wake-promoting agents that are distinguished from the traditional amphetamine scaffold by replacement of the N-alkyl substituent with a free primary amine and attachment of a carbamate ester on the propyl alcohol. The compound is unrelated at the scaffold level to modafinil, armodafinil, pitolisant, and the xanthine methyltransferase inhibitors (caffeine, theophylline), though it shares the dopamine-transporter pharmacology with modafinil at the molecular target level [1].

**Molecular formula:** C<sub>10</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub> (free base); C<sub>10</sub>H<sub>15</sub>ClN<sub>2</sub>O<sub>2</sub> (hydrochloride salt).

**Molecular weight:** 194.23 g/mol (free base); 230.69 g/mol (hydrochloride salt).

**Physical properties:** White to off-white crystalline powder. The hydrochloride salt is freely soluble in water and sparingly soluble in methanol and ethanol. The compound is stable at room temperature in solid form.

**Stereochemistry:** Solriamfetol contains one stereocenter at the 2-position of the propylamine chain and is supplied as the single (R)-enantiomer. The (S)-enantiomer has been characterized in preclinical assays and shows substantially reduced activity at DAT and NET. Investigators acquiring research-grade material should confirm enantiomeric purity by chiral chromatography or polarimetry.

## 1.3 Synthesis

Solriamfetol is derived from D-phenylalanine (the (R)-enantiomer of the natural amino acid). The published synthetic route proceeds through reduction of D-phenylalanine to (R)-2-amino-3-phenylpropan-1-ol (phenylalaninol), followed by selective carbamoylation of the primary alcohol with a carbamoylating agent such as carbonyl diimidazole or a chloroformate. The carbamate ester is formed selectively on the hydroxyl group in the presence of the free amine, which may be protected during the esterification step and subsequently deprotected. The hydrochloride salt is prepared by treatment with hydrogen chloride in a suitable solvent (diethyl ether, isopropanol, or dioxane) followed by recrystallization. Industrial syntheses optimize the carbamoylation step for regioselectivity and yield and control the enantiomeric purity through selection of the starting material rather than through late-stage chiral resolution, as D-phenylalanine is commercially available in high optical purity (greater than 99 percent enantiomeric excess) [2].

## 2. Abstract

Solriamfetol (JZP-110) is a selective dual dopamine and norepinephrine reuptake inhibitor (DNRI) and a trace amine-associated receptor 1 (TAAR1) agonist that was approved by the United States Food and Drug Administration on March 20, 2019 and by the European Medicines Agency on January 16, 2020 for the improvement of wakefulness and reduction of excessive daytime sleepiness (EDS) in adults with narcolepsy or obstructive sleep apnea (OSA) [3, 4]. The compound represents the first DNRI approved for these indications and is pharmacologically distinguished from the traditional psychostimulants (amphetamine, methylphenidate) by the absence of monoamine-releasing activity and from modafinil by its additional norepinephrine-transporter activity and TAAR1 agonism.

The clinical evidence base is anchored by the TONES (Treatment of Obstructive sleep apnea and Narcolepsy Excessive Sleepiness) program comprising five clinical trials. TONES 2 (Phase 3, narcolepsy, n = 231) and TONES 3 (Phase 3, OSA, n = 459) demonstrated statistically significant, dose-dependent improvements on the co-primary endpoints of MWT mean sleep latency and ESS score at 12 weeks [5, 6]. TONES 4 (randomized withdrawal in OSA) confirmed that cessation of treatment produces a return of sleepiness, supporting pharmacological rather than disease-modifying activity [7]. TONES 5 (52-week open-label extension, n = 643) confirmed maintenance of efficacy and tolerability on chronic dosing [8]. A meta-analysis of 1,177 patients across the randomized controlled trials reported an overall mean difference of 9.93 minutes on MWT and a 4.44-point reduction on ESS versus placebo [9].

The pharmacokinetic profile is defined by high oral bioavailability (approximately 95 percent), negligible hepatic metabolism, and predominant renal excretion of unchanged drug [10]. The absence of cytochrome P450-mediated metabolism eliminates the CYP-dependent drug interaction liability that characterizes many other CNS agents. The principal limitation of this pharmacokinetic profile is renal sensitivity: dose reduction is required in moderate renal impairment, the maximum dose is reduced in severe impairment, and the compound is not recommended in end-stage renal disease.

The compound is classified as a Schedule IV controlled substance in the United States, reflecting a measurable but low abuse potential relative to Schedule II stimulants [11]. The principal adverse events at approved doses are headache, nausea, decreased appetite, insomnia, and anxiety, with small dose-dependent increases in blood pressure and heart rate reflecting the noradrenergic mechanism.

## 3. Discovery and Development History

### 3.1 Origin

Solriamfetol was discovered at SK Biopharmaceuticals Co., Ltd., a subsidiary of the SK Group in South Korea. The compound emerged from a medicinal chemistry program focused on phenylalanine-derived dopamine and norepinephrine reuptake inhibitors designed to promote wakefulness without the monoamine-releasing properties of traditional psychostimulants. SK Biopharmaceuticals conducted the initial preclinical characterization and Phase 1 clinical pharmacokinetic and tolerability studies under the development code SKL-N05.

### 3.2 Licensing and development progression

In August 2011, following Phase 1 clinical trials, SK Biopharmaceuticals out-licensed the development and commercialization rights for solriamfetol (excluding certain Asian territories) to Aerial BioPharma, a North Carolina-based specialty pharmaceutical company, under the development code ADX-N05. Aerial BioPharma conducted additional clinical studies before the compound was acquired by Jazz Pharmaceuticals in 2014 under the development code JZP-110 [12]. Jazz Pharmaceuticals held worldwide development, manufacturing, and commercialization rights excluding 12 Asian markets retained by SK Biopharmaceuticals. Jazz Pharmaceuticals conducted the pivotal Phase 2 and Phase 3 clinical development program (the TONES studies) that supported regulatory submissions.

### 3.3 Regulatory approvals

The United States Food and Drug Administration approved solriamfetol (Sunosi) on March 20, 2019 for the improvement of wakefulness in adult patients with excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea [3]. Approved doses are 75 mg and 150 mg once daily for narcolepsy, and 37.5 mg, 75 mg, and 150 mg once daily for OSA. On June 17, 2019, the United States Drug Enforcement Administration placed solriamfetol in Schedule IV of the Controlled Substances Act on the basis of its abuse potential assessment [11].

The European Commission granted marketing authorization for Sunosi on January 16, 2020 to improve wakefulness and reduce excessive daytime sleepiness in adults with narcolepsy (with or without cataplexy) or OSA whose EDS has not been satisfactorily treated by primary OSA therapy [4]. The European approval included a contraindication in patients with recent myocardial infarction, serious cardiac arrhythmias, or other severe cardiac conditions, which is a precaution rather than a contraindication in the United States labeling.

### 3.4 Commercial transfer

In May 2022, Axsome Therapeutics acquired the rights to Sunosi from Jazz Pharmaceuticals for the United States and certain other markets, reflecting Jazz Pharmaceuticals' portfolio prioritization. Axsome assumed commercialization responsibilities and has continued marketing of the product [13]. SK Biopharmaceuticals retains rights in 12 Asian markets including the Republic of Korea, China, and Japan. The compound was the first Korean-originated central nervous system drug to receive FDA approval.

## 4. Mechanism of Action

Solriamfetol is a multi-target wake-promoting agent whose principal molecular activities are inhibition of the dopamine transporter (DAT), inhibition of the norepinephrine transporter (NET), and agonism at the trace amine-associated receptor 1 (TAAR1). These activities operate at overlapping concentration ranges achieved at approved oral doses and contribute to the wake-promoting, alertness-enhancing, and potentially mood-modulating effects of the compound.

### 4.1 Dopamine transporter inhibition

Solriamfetol inhibits the human dopamine transporter with an IC<sub>50</sub> of approximately 2.9 micromolar and a binding affinity (K<sub>i</sub>) of approximately 14.2 micromolar [1]. The inhibition prevents the reuptake of synaptic dopamine into the presynaptic terminal, elevating extracellular dopamine concentrations in the nucleus accumbens, striatum, and prefrontal cortex. This mechanism is shared with modafinil and methylphenidate at the molecular-target level, though solriamfetol differs from amphetamine and methamphetamine in that it does not promote vesicular release or reverse transporter flux. The distinction between reuptake inhibition and release is pharmacologically meaningful: releasing agents produce larger, less physiologically constrained increases in synaptic monoamines and carry correspondingly higher abuse liability and peripheral sympathomimetic risk.

### 4.2 Norepinephrine transporter inhibition

Solriamfetol inhibits the human norepinephrine transporter with an IC<sub>50</sub> of approximately 4.4 micromolar and a binding affinity (K<sub>i</sub>) of approximately 3.7 micromolar [1]. This dual DAT-NET inhibition distinguishes solriamfetol from modafinil, which acts predominantly at DAT with relatively weak NET activity, and from atomoxetine, which is a selective NET inhibitor with minimal DAT activity. The norepinephrine-transporter inhibition produces elevated extracellular norepinephrine in the locus coeruleus projection fields, including the prefrontal cortex, thalamus, and hypothalamic wake-promoting nuclei. The noradrenergic contribution to the

wake-promoting mechanism is consistent with the established role of the ascending noradrenergic arousal system originating from the locus coeruleus in the maintenance of wakefulness and alertness [14].

### 4.3 Serotonin transporter selectivity

Solriamfetol has weak affinity for the serotonin transporter ( $K_i$  approximately 81.5 micromolar) and does not appreciably inhibit serotonin reuptake at clinically relevant concentrations ( $IC_{50}$  greater than 100 micromolar) [1]. The selectivity for DAT and NET over SERT (approximately 20- to 30-fold) is a defining pharmacological characteristic of the compound and separates it from the serotonin-norepinephrine reuptake inhibitors (venlafaxine, duloxetine) and from the triple reuptake inhibitors studied in depression.

### 4.4 Trace amine-associated receptor 1 agonism

In addition to transporter inhibition, solriamfetol acts as an agonist at the human trace amine-associated receptor 1 (hTAAR1) with an  $EC_{50}$  of approximately 10 to 16 micromolar [15]. TAAR1 is an intracellular G protein-coupled receptor expressed in dopaminergic neurons of the ventral tegmental area (VTA), in the dorsal raphe, and in other monoaminergic nuclei. Activation of TAAR1 modulates dopaminergic neuron firing through a cascade involving adenylate cyclase activation, cAMP elevation, and downstream phosphorylation of the dopamine transporter itself, which can reduce DAT surface expression and further augment synaptic dopamine concentrations. The TAAR1  $EC_{50}$  of solriamfetol overlaps with its DAT and NET inhibitory potencies and falls within the clinically observed therapeutic plasma concentration range, suggesting that TAAR1 agonism contributes to the pharmacological effect at approved doses [15].

Electrophysiology studies in mouse ventral tegmental area brain slices demonstrated that solriamfetol (1 to 10 micromolar) dose-dependently inhibited the firing frequency of dopaminergic VTA neurons, a pattern consistent with TAAR1 agonist activity and distinct from the excitatory effects of traditional psychostimulants at the same neurons [15].

## 4.5 Absence of monoamine-releasing activity

A critical pharmacological distinction of solriamfetol is its lack of monoamine-releasing activity. In in vitro superfusion assays with [3H]-dopamine-loaded and [3H]-norepinephrine-loaded synaptosomes, solriamfetol did not promote calcium-independent reverse transport of labeled monoamines, in contrast to amphetamine which produced dose-dependent release [1]. In vivo microdialysis studies in rat nucleus accumbens confirmed that solriamfetol elevates extracellular dopamine through reuptake inhibition rather than release, producing a quantitatively and temporally distinct neurochemical profile compared to amphetamine [1]. This distinction is the pharmacological basis for the lower abuse potential and the absence of the peripheral sympathomimetic surges that characterize amphetamine-type stimulants.

## 4.6 Behavioral pharmacology and locomotor profile

In preclinical behavioral models, solriamfetol promoted wakefulness and reduced sleep propensity in sleep-deprived and narcoleptic mouse models. Notably, unlike amphetamine and modafinil, solriamfetol did not produce significant hyperlocomotion in naive mice at wake-promoting doses, suggesting that its arousal-enhancing effect can be separated from the general locomotor activation produced by traditional psychostimulants [16]. In DAT knockout mice, solriamfetol inhibited rather than stimulated locomotor activity, a pattern characteristic of TAAR1 agonists and opposite to the effect of releasing agents in the same model [15]. A comparison study in narcoleptic (orexin-deficient) mice found that 150 mg/kg solriamfetol did not produce the anxiety-related behaviors observed with 100 mg/kg modafinil [17].

## 5. Pharmacokinetics and Routes of Administration

### 5.1 Absorption

Solriamfetol is rapidly and almost completely absorbed after oral administration. Oral bioavailability is approximately 95 percent [10]. The median time to peak plasma concentration (T<sub>max</sub>) is approximately 2 hours, with a range of 1.25 to 3.0 hours. A high-fat meal modestly delays T<sub>max</sub> by approximately 1 hour without meaningfully affecting peak concentration (C<sub>max</sub>) or total exposure (AUC), and the compound may therefore be administered without regard to food [10]. Peak plasma concentration after a 150 mg oral dose is approximately 7 to 8 micrograms per milliliter.

### 5.2 Distribution

Solriamfetol has a moderate volume of distribution. Plasma protein binding is low (approximately 13 to 19 percent), which is a distinctive feature of the compound relative to most CNS agents and is consistent with its predominantly renal elimination pathway [10]. The low protein binding means that changes in plasma protein levels (in hepatic disease, nephrotic syndrome, or hypoalbuminemic states) have minimal effect on free drug concentration. The compound crosses the blood-brain barrier; central nervous system penetration is sufficient to produce the observed wake-promoting effects, though quantitative human CNS distribution data from positron emission tomography or cerebrospinal fluid studies have not been published as of the most recent monograph revision.

### 5.3 Metabolism

Solriamfetol is minimally metabolized in humans. The only identified metabolite is N-acetyl solriamfetol, which is pharmacologically inactive and accounts for less than 1 percent of the administered dose recovered in urine [10]. The compound does not undergo appreciable cytochrome P450-mediated phase 1 metabolism. In vitro studies confirm that solriamfetol is not a substrate, inhibitor, or inducer of the

major CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4) at clinically relevant concentrations [10]. This negligible metabolic transformation is the basis for the absence of CYP-mediated drug-drug interaction liability and is a substantial clinical advantage in patients receiving polypharmacy for comorbid conditions.

## 5.4 Elimination

Solriamfetol is eliminated predominantly by the kidneys. Approximately 95 percent of an administered dose is recovered in urine as unchanged parent compound, and less than 1 percent as N-acetyl solriamfetol [10]. The elimination follows first-order kinetics with a terminal elimination half-life of approximately 7.1 hours in subjects with normal renal function. Renal clearance accounts for the majority of apparent total clearance and exceeds the creatinine clearance by approximately 3-fold, indicating that active tubular secretion is the major elimination mechanism rather than glomerular filtration alone [10].

The renal elimination pathway makes the compound sensitive to renal impairment. The half-life of solriamfetol increases approximately 1.2-fold in mild renal impairment (estimated glomerular filtration rate 60 to 89 mL/min), 1.9-fold in moderate impairment (eGFR 30 to 59 mL/min), and 3.9-fold in severe impairment (eGFR 15 to 29 mL/min) [10]. In end-stage renal disease, the compound accumulates substantially, and administration is not recommended. Dose adjustment is required in moderate and severe renal impairment (maximum recommended dose of 75 mg once daily in moderate impairment and 37.5 mg once daily in severe impairment).

## 5.5 Routes of administration

Solriamfetol is administered exclusively by the oral route in approved formulations. The marketed product (Sunosi) is supplied as immediate-release tablets in 75 mg and 150 mg strengths, with the 37.5 mg dose for OSA achieved by tablet splitting of the 75 mg tablet. The compound should be taken upon awakening in the morning, and late-in-the-day dosing should be avoided because of the risk of insomnia. No parenteral, intravenous, or alternative route formulations have been developed for clinical use. For research applications, the hydrochloride salt is freely soluble in water and can be prepared as aqueous solutions for in vitro or animal dosing.

## 5.6 Special populations

**Renal impairment:** As described above, dose reduction is required. The prescribing label specifies a maximum dose of 75 mg in moderate renal impairment and 37.5 mg in severe impairment. The compound is not recommended in end-stage renal disease (eGFR less than 15 mL/min) [10].

**Hepatic impairment:** Because solriamfetol undergoes negligible hepatic metabolism, hepatic impairment (including severe hepatic impairment, Child-Pugh C) does not meaningfully affect the pharmacokinetics, and no dose adjustment is required [10].

**Elderly:** Age-related decline in renal function may affect solriamfetol elimination. Dose selection should consider renal function rather than age per se. No age-specific dose adjustment is required beyond what is dictated by renal function.

**Pediatric:** Solriamfetol is not approved for pediatric use. Safety and efficacy have not been established in patients younger than 18 years.

**Pregnancy and lactation:** There are no adequate data on the use of solriamfetol in pregnant women. Animal reproduction studies at doses producing exposures greater than 3 times the maximum recommended human dose did not demonstrate teratogenicity but showed reduced pup survival at high doses. The compound is classified as pregnancy risk summary "insufficient data" in the current labeling. Solriamfetol and its metabolites are present in rat milk; it is not known whether the compound is excreted in human milk [10].

## 6. Preclinical Pharmacology

### 6.1 In vitro transporter pharmacology

The foundational in vitro characterization of solriamfetol was published by Baladi et al. (2018) in the Journal of Pharmacology and Experimental Therapeutics [1]. In human embryonic kidney (HEK293) cells stably expressing the human dopamine transporter (hDAT), human norepinephrine transporter (hNET), or human serotonin transporter (hSERT), solriamfetol inhibited [3H]-dopamine uptake with an IC<sub>50</sub> of 2.9 micromolar, [3H]-norepinephrine uptake with an IC<sub>50</sub> of 4.4 micromolar, and showed negligible inhibition of [3H]-serotonin uptake (IC<sub>50</sub> greater than 100 micromolar). Radioligand binding at DAT (K<sub>i</sub> 14.2 micromolar), NET (K<sub>i</sub> 3.7 micromolar), and SERT (K<sub>i</sub> 81.5 micromolar) confirmed the selectivity profile [1].

In the same study, solriamfetol was tested at more than 50 additional receptors, ion channels, and enzymes in a broad pharmacological screen and showed no significant binding or functional activity (less than 50 percent displacement at 10 micromolar) at any non-target site, confirming a clean off-target pharmacology profile relative to the amphetamines and many other CNS-active agents [1].

### 6.2 In vivo neurochemistry

Microdialysis studies in freely moving rats demonstrated that solriamfetol (10 to 30 mg/kg intraperitoneal) produced dose-dependent increases in extracellular dopamine in the nucleus accumbens and in extracellular norepinephrine in the prefrontal cortex [1]. The magnitude and time course of the dopamine elevation were consistent with reuptake inhibition rather than release. In contrast to amphetamine, which produced a rapid, large-magnitude dopamine surge, solriamfetol produced a more gradual and sustained elevation, peaking approximately 60 to 90 minutes post-injection and declining over 3 to 4 hours.

## 6.3 Wake-promoting activity

In mouse sleep/wake studies using electroencephalography and electromyography (EEG/EMG) telemetry, solriamfetol dose-dependently increased the duration of wakefulness and decreased the duration of non-rapid-eye-movement (NREM) sleep during the active treatment period [15]. The wake-promoting activity was present at doses that did not produce hyperlocomotion, supporting a dissociation between wakefulness enhancement and general locomotor stimulation. In orexin-knockout mice (a genetic model of narcolepsy type 1), solriamfetol reduced the frequency and duration of cataplexy-like episodes, providing preclinical evidence for efficacy in the narcolepsy phenotype [17].

## 6.4 TAAR1 electrophysiology

The TAAR1 pharmacology of solriamfetol was characterized in ventral tegmental area brain slice preparations [15]. Solriamfetol at concentrations of 1, 3, and 10 micromolar dose-dependently inhibited the spontaneous firing rate of dopaminergic VTA neurons, a signature of TAAR1 agonist activity also observed with the selective TAAR1 agonist RO5166017. The inhibitory effect was blocked by the TAAR1 antagonist EPPTB, confirming target engagement. In DAT knockout mice, solriamfetol paradoxically reduced locomotor activity, consistent with the TAAR1-mediated inhibitory mechanism and opposite to the behavioral effect of releasing agents in the same model [15].

## 6.5 Comparison with other wake-promoting agents in pre-clinical models

A comparative preclinical study by Krief et al. (2021) examined solriamfetol alongside amphetamine, modafinil, and pitolisant in standardized behavioral and neurochemical assays [16]. All three monoaminergic agents (amphetamine, modafinil, solriamfetol) increased extracellular dopamine in the nucleus accumbens and produced behavioral sensitization on repeated dosing, whereas pitolisant (a histamine H3 receptor inverse agonist) was devoid of such effects. Within the monoaminergic group, solriamfetol produced dopamine elevations intermediate between modafinil (lower) and amphetamine (higher), and behavioral sensitization less pronounced than amphetamine. These findings positioned solriamfetol between modafinil and amphetamine in the neurochemical and behavioral spectrum of wake-promoting agents [16].

## 7. Clinical Evidence Base

### 7.1 TONES 2: Narcolepsy Phase 3

The TONES 2 study (NCT02348593) was a 12-week, randomized, double-blind, placebo-controlled Phase 3 trial evaluating solriamfetol 75, 150, and 300 mg once daily in 231 adults with narcolepsy (type 1 or type 2) with EDS [5]. Eligible patients had a mean sleep latency of less than 25 minutes on the MWT, an ESS score of 10 or greater, and usual nightly sleep of 6 hours or more. The 300 mg dose was studied for efficacy but is not a labeled dose.

**Co-primary endpoints:** Change from baseline to week 12 in MWT mean sleep latency and ESS score.

**Results:** Solriamfetol at 300 mg and 150 mg produced statistically significant improvements on both co-primary endpoints. The least-squares mean change from baseline in MWT sleep latency at week 12 was 12.3 minutes (SE 1.4) for 300 mg, 9.8 minutes (SE 1.3) for 150 mg, 4.7 minutes (SE 1.4) for 75 mg, and 2.1 minutes (SE 1.3) for placebo. The 300 mg and 150 mg doses were statistically superior to placebo ( $p$  less than 0.001); the 75 mg dose was not statistically significant after multiplicity adjustment. ESS reductions were similarly dose-dependent, with 49.2 percent of patients achieving an ESS score of 10 or below (the normal range) at 300 mg compared with 15.5 percent on placebo [5].

**Patient Global Impression of Change (PGI-C):** A significantly greater proportion of patients rated themselves as "much improved" or "very much improved" at 150 mg and 300 mg compared with placebo.

### 7.2 TONES 3: Obstructive sleep apnea Phase 3

The TONES 3 study (NCT02348606) was a 12-week, randomized, double-blind, placebo-controlled Phase 3 trial evaluating solriamfetol 37.5, 75, 150, and 300 mg once daily in 459 adults with OSA and residual EDS despite adequate use or attempted use of primary OSA therapy (continuous positive airway pressure or other) [6]. The 37.5 mg and 300 mg doses were studied for efficacy but are not labeled doses in all jurisdictions.

**Results:** Solriamfetol at 300, 150, and 75 mg doses produced statistically significant improvements on MWT and ESS co-primary endpoints. The 37.5 mg dose produced a modest, non-significant effect. MWT mean sleep latency increased by approximately 10 to 13 minutes at the 150 mg and 300 mg doses, and ESS decreased by approximately 3.8 to 4.9 points compared with approximately 0.8 to 1.6 points for placebo [6]. Efficacy was observed regardless of whether patients were adherent or nonadherent to primary airway therapy, supporting the independence of the wake-promoting effect from OSA disease modification [18].

## 7.3 TONES 4: Randomized withdrawal in OSA

TONES 4 was a 6-week, randomized, double-blind, placebo-controlled withdrawal study in patients with OSA who had completed a prior open-label solriamfetol treatment period [7]. Patients who were stable on solriamfetol were randomized to continue solriamfetol or switch to placebo. Those switched to placebo experienced significant worsening on MWT and ESS relative to those continuing solriamfetol, confirming that the wake-promoting effect requires continued drug exposure and is not attributable to a practice effect, a sustained disease-modifying mechanism, or a conditioned response.

## 7.4 TONES 5: Long-term open-label extension

The TONES 5 study was a 52-week, open-label, flexible-dose extension study in 643 participants with narcolepsy (n = 226) or OSA (n = 417) who had completed a prior TONES study [8]. Participants could receive solriamfetol 75, 150, or 300 mg once daily. The study confirmed long-term maintenance of efficacy, with ESS and MWT improvements sustained through 52 weeks of dosing. The safety profile was consistent with the shorter-term studies, with no new safety signals emerging on chronic exposure. A randomized withdrawal phase within TONES 5 confirmed the pharmacological dependence of the effect: participants who continued solriamfetol maintained their ESS improvement (LS mean change of 1.6 points), whereas those switched to placebo worsened (LS mean change of 5.3 points) [8].

## 7.5 Meta-analytic evidence

A systematic review and meta-analysis by Xiang et al. (2021) pooling data from 1,177 participants across five randomized controlled trials reported an overall weighted mean difference for MWT mean sleep latency of 9.93 minutes (95 percent

CI 7.25 to 12.62) and for ESS score of negative 4.44 points (95 percent CI negative 5.76 to negative 3.12), both statistically significant in favor of solriamfetol [9]. The number needed to treat for a clinically meaningful ESS response (defined as a score of 10 or less) ranged from approximately 3 to 6 depending on dose and indication.

## 7.6 Special populations and subgroup analyses

Post-hoc analyses of the TONES data have evaluated solriamfetol efficacy in participants with comorbid depression, in participants nonadherent to primary OSA therapy, and across demographic subgroups. Efficacy was generally consistent across subgroups, including participants with a history of depression, in whom solriamfetol improved EDS without worsening depressive symptoms [19]. Participants with OSA who were not adherent to CPAP or other primary therapy experienced wake-promoting benefit similar to adherent participants [18].

## 8. Sourcing and Quality Verification

Pharmaceutical-grade solriamfetol is available as the marketed product Sunosi in the United States, European Union member states, and selected other jurisdictions. The marketed formulation is an immediate-release tablet containing solriamfetol hydrochloride equivalent to 75 mg or 150 mg of solriamfetol free base. Investigators requiring pharmaceutical-grade material for clinical research should source through registered pharmaceutical distributors.

Research-grade solriamfetol hydrochloride is supplied by multiple chemical and pharmaceutical research suppliers (Sigma-Aldrich, Cayman Chemical, MedChemExpress, Selleckchem, Toronto Research Chemicals, others) at greater than 98 percent purity by HPLC. Supply is typically in milligram to gram quantities as the hydrochloride salt.

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

- High-performance liquid chromatography area-percent purity, ideally greater than 98 percent
- Mass spectrometry confirmation of molecular weight (195.23 for the protonated free base  $[M+H]^+$ , or 231.69 for the hydrochloride including the chloride ion)
- Chiral HPLC or polarimetry confirmation of enantiomeric purity (greater than 99 percent enantiomeric excess of the (R)-form)
- Karl Fischer or loss-on-drying analysis for residual water
- Residual solvent analysis by gas chromatography

Third-party analytical confirmation (Janoshik Analytical or equivalent independent laboratories) is appropriate for any investigation requiring dose-response precision. The research-grade solriamfetol market is smaller than that of modafinil or amphetamine analogs, and lot-to-lot variability should be anticipated.

## 9. Reconstitution and Handling

Solriamfetol hydrochloride is freely soluble in water at room temperature. For in vitro research applications, the compound is supplied as a crystalline powder and is reconstituted in aqueous buffer (phosphate-buffered saline, artificial cerebrospinal fluid, or cell culture medium) at concentrations typically ranging from 1 to 100 millimolar stock solutions. Dimethyl sulfoxide (DMSO) stock solutions at 10 to 100 millimolar are acceptable where higher stock concentrations are required; the DMSO concentration in the final assay should be kept below 0.1 to 0.3 percent to avoid solvent effects.

For in vivo research applications in rodents, the compound is dissolved in normal saline or in 5 percent dextrose solution at the required concentration for intraperitoneal, oral gavage, or subcutaneous administration. Dose ranges in the pre-clinical literature span 3 to 150 mg/kg in mice and 1 to 30 mg/kg in rats, depending on the endpoint.

Storage of the solid compound at room temperature (15 to 25 degrees Celsius) in a dry, light-protected environment is adequate for long-term stability. Aqueous stock solutions should be prepared fresh or stored at 2 to 8 degrees Celsius and used within 7 to 14 days. Freeze-thaw cycles should be minimized; aliquoting of stock solution for single-use is recommended.

The compound is classified as Schedule IV in the United States, and investigators in the United States should ensure appropriate DEA registration and record-keeping for receipt, storage, and use. In other jurisdictions, controlled-substance regulations may differ and should be confirmed with the relevant regulatory authority.

## 10. Stack Interactions and Combinations

Solriamfetol has a distinctive drug interaction profile that reflects its minimal hepatic metabolism and its dopaminergic/noradrenergic mechanism. The principal interaction considerations are pharmacodynamic rather than pharmacokinetic.

**Monoamine oxidase inhibitors (MAOIs):** Concurrent use with MAOIs (phenelzine, tranylcypromine, selegiline at doses above 6 mg transdermal, isocarboxazid, linezolid, methylene blue) is contraindicated. MAOIs prevent the degradation of synaptic dopamine and norepinephrine, and the addition of a reuptake inhibitor produces the potential for severe hypertensive crisis, serotonin syndrome analogs, and cardiovascular emergency. Solriamfetol must not be administered during or within 14 days of MAOI discontinuation [10].

**Other dopaminergic agents:** Concurrent use with other dopamine-elevating agents (levodopa/carbidopa, pramipexole, ropinirole, amphetamine, methylphenidate, bupropion, modafinil) produces additive dopaminergic activity. The combination may increase the risk of adverse events including nausea, tachycardia, agitation, and psychomotor activation. Dose adjustment of one or both agents may be appropriate in clinical or research contexts where combination is necessary.

**Norepinephrine-elevating agents:** Concurrent use with norepinephrine reuptake inhibitors (atomoxetine, venlafaxine, duloxetine, tricyclic antidepressants) or with norepinephrine-releasing agents produces additive noradrenergic activity and may increase the risk of hypertension, tachycardia, and anxiety.

**Antihypertensive agents:** The blood pressure-elevating effect of solriamfetol may partially oppose the efficacy of antihypertensive therapy. Blood pressure should be monitored when initiating solriamfetol in patients on antihypertensive medications, and dose adjustments of antihypertensive agents may be needed.

**CYP-mediated interactions:** Because solriamfetol is neither a substrate, inhibitor, nor inducer of the major cytochrome P450 enzymes, it does not participate in the CYP-mediated drug interaction network [10]. This is a substantial practical

advantage over modafinil (which induces CYP3A4 and can reduce the efficacy of hormonal contraceptives and other CYP3A4 substrates) and over methylphenidate (which can inhibit CYP2D6 at high concentrations).

**Renal transporter interactions:** Solriamfetol is actively secreted by renal tubular transporters. Compounds that inhibit renal organic cation transporters (OCT2, MATE1, MATE2-K) may theoretically reduce solriamfetol renal clearance and increase plasma exposure, though clinically significant interactions through this pathway have not been characterized in published studies.

**Sedative-hypnotic agents:** The wake-promoting effect of solriamfetol may partially oppose the sedative effects of benzodiazepines, non-benzodiazepine hypnotics (zolpidem, suvorexant), and antihistamines. In clinical practice, the concurrent use of a wake-promoting agent during the day and a sedative-hypnotic at night is common in narcolepsy management and is not contraindicated, provided the dosing schedule separates the two pharmacological effects temporally.

# 11. Adverse Events and Safety

## 11.1 Common adverse events

The principal adverse events at approved doses, pooled across the Phase 3 TONES 2 and TONES 3 trials, are [5, 6, 10]:

- Headache (approximately 8 to 11 percent at 150 mg, dose-dependent)
- Nausea (approximately 6 to 8 percent)
- Decreased appetite (approximately 4 to 9 percent, dose-dependent)
- Insomnia (approximately 4 to 6 percent)
- Anxiety (approximately 3 to 6 percent)
- Nasopharyngitis (approximately 3 to 4 percent)
- Dizziness (approximately 2 to 4 percent)
- Dry mouth (approximately 2 to 3 percent)

An analysis of the incidence and duration of early-onset adverse events by Malhotra et al. (2022) demonstrated that most common adverse events (headache, nausea, decreased appetite) emerged within the first two weeks of treatment and were generally mild to moderate, with a median duration of approximately 2 to 3 weeks, and many resolved despite continued treatment [20].

## 11.2 Cardiovascular effects

Solriamfetol produces dose-dependent increases in systolic blood pressure (mean 0.5 to 2.5 mmHg), diastolic blood pressure (mean negative 0.2 to 1.5 mmHg), and heart rate (mean 0.7 to 2.9 beats per minute) measured over 9 hours post-dose, with the highest increases associated with the 300 mg dose [10]. These cardiovascular effects are small in magnitude at the population level but may be clinically meaningful in individual patients with pre-existing hypertension, cardiovascular disease, or risk factors for major adverse cardiovascular events.

The prescribing label recommends assessment of blood pressure prior to initiating treatment and periodic monitoring during treatment. New-onset hypertension and exacerbations of pre-existing hypertension should be treated. In the European

Union, the compound is contraindicated in patients with recent myocardial infarction, serious cardiac arrhythmias, or other severe cardiac conditions [4]. In the United States, the compound is not recommended (but is not formally contraindicated) in patients with unstable or severe cardiovascular disease.

A thorough QTc study (Zomorodi et al. 2021) evaluated solriamfetol at therapeutic (150 mg) and supratherapeutic (600 mg) doses in a 4-period crossover design with positive control (moxifloxacin) [21]. Solriamfetol did not produce clinically meaningful QTc prolongation at either dose, and the study excluded a QTc effect exceeding 10 milliseconds at the upper bound of the one-sided 95 percent confidence interval.

### 11.3 Psychiatric effects

Anxiety and insomnia are dose-dependent adverse events reflecting the noradrenergic and dopaminergic mechanism. Postmarketing surveillance has additionally identified reports of depression, suicidal ideation, irritability, and agitation, though causal attribution is complicated by the psychiatric comorbidity prevalent in narcolepsy and OSA populations [22]. The prescribing label includes a warning regarding psychiatric symptoms and advises monitoring for new or worsening psychiatric symptoms during treatment.

### 11.4 Abuse potential

A human abuse potential study evaluated subjective drug-liking responses to solriamfetol at doses of 300, 600, and 1,200 mg (2 to 8 times the maximum recommended dose) compared with phentermine 60 mg (positive control) and placebo in recreational stimulant users [11]. Solriamfetol produced dose-dependent increases in drug-liking and euphoria scores, with responses at supratherapeutic doses similar in magnitude to phentermine. At the approved dose range (75 to 150 mg), drug-liking was substantially lower. On the basis of this assessment and the totality of the preclinical and clinical data, the DEA placed solriamfetol in Schedule IV, the same schedule as modafinil, indicating accepted medical use and low abuse potential that may lead to limited physical or psychological dependence [11].

## 11.5 Withdrawal and rebound

Abrupt discontinuation of solriamfetol after chronic dosing does not produce a classical withdrawal syndrome. The TONES 4 and TONES 5 randomized withdrawal data demonstrated that cessation produces a return of baseline sleepiness rather than a rebound worsening beyond the pre-treatment level [7, 8]. No seizures, autonomic instability, or other serious discontinuation events were observed in the clinical trials.

## 11.6 Pregnancy, lactation, and fertility

Animal reproduction studies at exposures exceeding 3 times the maximum recommended human dose did not demonstrate teratogenicity. Reduced pup survival was observed at high doses. There are no adequate data in pregnant women, and the compound should be used during pregnancy only if the potential benefit justifies the potential risk. The compound is present in rat milk; excretion in human milk is unknown. Fertility studies in rats did not demonstrate adverse effects on male or female fertility at clinically relevant exposures [10].

## 12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five wake-promoting agents against solriamfetol, evaluated on five competency standards: novelty, effect size, promising potential, side-effect profile, and overall validation. The five comparators were selected as the principal pharmacological alternatives for EDS in narcolepsy and OSA, spanning the mechanistic spectrum from dopamine reuptake inhibition to histamine modulation to adrenergic receptor agonism.

### 12.1 Modafinil (Provigil)

**Mechanism:** Dopamine reuptake inhibitor (DAT-selective) with uncertain ancillary mechanisms. The precise mechanism of wake promotion remains incompletely characterized despite decades of clinical use, though DAT binding is the established primary target. Modafinil lacks appreciable NET activity and does not act at TAAR1 [23].

**Novelty:** Low. Modafinil has been the standard of care for EDS in narcolepsy since its FDA approval in 1998 and for residual EDS in OSA since 2004. The mechanism, though still debated in detail, is well established. It represents the reference compound against which newer agents are measured.

**Effect size:** Meta-analytic evidence from the Cochrane Collaboration and subsequent systematic reviews places modafinil approximately 2.5 to 3.5 ESS points superior to placebo in narcolepsy and OSA, somewhat less than the 4.4-point advantage reported for solriamfetol in pooled analyses [9, 24]. An indirect treatment comparison by Boof et al. (2022) confirmed that solriamfetol had a greater ESS effect size than modafinil-armodafinil (difference of approximately 1.0 to 1.5 ESS points) in the OSA population [25].

**Promising potential:** Moderate. Modafinil is well established and widely prescribed but is now off-patent with extensive generic competition. No new clinical development is anticipated. Its positioning is as a first-line standard of care rather than a pipeline agent.

**Side-effect profile:** The principal adverse events are headache, nausea, anxiety, and insomnia. Modafinil induces CYP3A4 and reduces the efficacy of hormonal contraceptives. Rare serious adverse events include Stevens-Johnson syndrome, toxic epidermal necrolysis, and multi-organ hypersensitivity reaction; these carry a warning in the prescribing label. Modafinil is Schedule IV.

**Overall validation:** High. Decades of clinical use, extensive pharmacovigilance data, and meta-analytic evidence support the efficacy and safety of modafinil. It is the most validated compound in the class.

**Comparison to solriamfetol:** Solriamfetol has a modestly greater ESS effect size in indirect comparisons, a cleaner drug interaction profile (no CYP induction), additional NET activity and TAAR1 agonism, and the absence of the rare dermatologic hypersensitivity signal. Modafinil has the advantages of longer clinical experience, established generic availability, and broader prescribing familiarity.

## 12.2 Armodafinil (Nuvigil)

**Mechanism:** The (R)-enantiomer of modafinil with the same DAT-selective mechanism. Armodafinil has a longer effective half-life than racemic modafinil owing to the slower clearance of the (R)-enantiomer relative to the (S)-enantiomer, producing higher plasma concentrations in the later portions of the dosing interval.

**Novelty:** Low. Armodafinil is essentially a single-enantiomer reformulation of modafinil and does not represent a novel mechanism.

**Effect size:** Similar to modafinil. The indirect treatment comparison by Boof et al. (2022) grouped armodafinil with modafinil and found solriamfetol superior to the combined modafinil-armodafinil group on ESS endpoints [25].

**Promising potential:** Low. The compound is off-patent, with generic availability. No new clinical development.

**Side-effect profile:** Similar to modafinil, including the CYP3A4 induction liability and the rare dermatologic hypersensitivity risk. Schedule IV.

**Overall validation:** High, equivalent to modafinil.

**Comparison to solriamfetol:** The same differential as modafinil applies. The longer effective half-life of armodafinil may be an advantage for late-day wakefulness but a disadvantage for insomnia risk; solriamfetol's 7.1-hour half-life provides

an intermediate duration of effect.

## 12.3 Pitolisant (Wakix)

**Mechanism:** Histamine H3 receptor inverse agonist/antagonist. Pitolisant blocks the presynaptic H3 autoreceptor on histaminergic neurons of the tuberomammillary nucleus, thereby disinhibiting histamine release and enhancing histaminergic wake signaling [26]. The mechanism is entirely distinct from the dopaminergic/noradrenergic mechanism of solriamfetol.

**Novelty:** High. Pitolisant is the first and only histamine-based wake-promoting agent approved for narcolepsy (FDA approval 2019, same year as solriamfetol). The histaminergic mechanism is orthogonal to dopaminergic approaches and represents a genuinely novel therapeutic concept.

**Effect size:** Clinical trial data demonstrate ESS improvements of approximately 3 to 5 points versus placebo in narcolepsy, broadly similar to modafinil and somewhat less than solriamfetol in indirect comparisons [26]. A network meta-analysis by Sun et al. (2023) in *Annals of Internal Medicine* ranked solriamfetol first among wake-promoting agents for both MWT and ESS outcomes in OSA, with pitolisant ranked lower on both measures [27].

**Promising potential:** Moderate to high. Pitolisant is approved for narcolepsy (not for OSA in the United States). It has no abuse potential classification (it is not a scheduled substance in the United States), which is a commercial and clinical advantage. Active investigation continues for OSA, idiopathic hypersomnia, and Prader-Willi syndrome.

**Side-effect profile:** The principal adverse events are insomnia, headache, and nausea. Pitolisant does not produce significant blood pressure or heart rate increases. It does prolong QTc at supratherapeutic doses and carries a warning for QTc prolongation. It is a CYP2D6 inhibitor and CYP3A4 inducer, producing drug interaction considerations. Critically, pitolisant is not a controlled substance.

**Overall validation:** Moderate. Approved for narcolepsy with a growing evidence base. The non-scheduled status is a major practical advantage.

**Comparison to solriamfetol:** Solriamfetol has a greater ESS effect size in indirect comparisons and a broader approved indication (both narcolepsy and OSA). Pitolisant has the advantages of a non-dopaminergic mechanism, no controlled-

substance classification, no blood pressure elevation, and a potential role for cataplexy reduction (approved for this in the EU). The two agents may be mechanistically complementary for combination investigation.

## 12.4 Methylphenidate (Ritalin, Concerta)

**Mechanism:** Dopamine and norepinephrine reuptake inhibitor with weak monoamine-releasing activity at higher concentrations. Methylphenidate shares the DAT and NET transporter targets with solriamfetol but differs in its partial releasing-agent properties and in its substantially higher abuse liability [28].

**Novelty:** Low. Methylphenidate has been used for narcolepsy since the 1950s and for attention-deficit/hyperactivity disorder since 1955. It is the oldest agent in this comparator panel.

**Effect size:** Methylphenidate is effective for EDS in narcolepsy, though contemporary randomized controlled trial data comparable to the TONES program are limited. Historical clinical experience and smaller trials support efficacy for daytime alertness, but the evidence base does not meet the standards of modern registration trials.

**Promising potential:** Low for narcolepsy/OSA specifically. The compound is widely used off-label but has been largely supplanted by modafinil and newer agents in narcolepsy guidelines. Its primary clinical positioning is in ADHD.

**Side-effect profile:** The principal adverse events include insomnia, decreased appetite, headache, tachycardia, hypertension, and anxiety. Methylphenidate carries the sympathomimetic cardiovascular risk profile associated with dopaminergic/noradrenergic stimulants and has a higher abuse potential than solriamfetol (Schedule II versus Schedule IV). Growth suppression is a concern in pediatric ADHD populations.

**Overall validation:** Moderate for EDS indications. Extensive clinical use but limited modern trial evidence for narcolepsy. High validation for ADHD.

**Comparison to solriamfetol:** Solriamfetol has a more favorable abuse-potential profile (Schedule IV versus Schedule II), the absence of monoamine-releasing activity, a cleaner drug interaction profile, and a modern registration-quality evidence

base for narcolepsy and OSA. Methylphenidate has the advantages of decades of clinical experience, multiple formulations (immediate-release, extended-release, osmotic-release), and very low cost.

## 12.5 Sodium oxybate (Xyrem, Xywav)

**Mechanism:** Gamma-hydroxybutyrate (GHB) acting at GABA-B receptors and GHB receptors. Sodium oxybate is a nighttime-administered sedative that consolidates nocturnal sleep and, through improved sleep architecture, reduces daytime sleepiness and cataplexy in narcolepsy [29]. The mechanism of wake promotion is therefore indirect (via improved sleep quality) rather than direct (via monoaminergic arousal stimulation), making it mechanistically orthogonal to solriamfetol.

**Novelty:** Moderate. The GHB mechanism for narcolepsy was a novel therapeutic concept when sodium oxybate was approved in 2002, though the compound has now been in clinical use for over two decades.

**Effect size:** Sodium oxybate is the most effective single agent for narcolepsy cataplexy reduction and produces ESS improvements of approximately 3 to 5 points in randomized trials. For EDS alone (without cataplexy), the effect size is broadly comparable to modafinil and somewhat less than solriamfetol on direct daytime wakefulness measures. However, sodium oxybate addresses cataplexy, fragmented nighttime sleep, and sleep paralysis, which solriamfetol does not.

**Promising potential:** Moderate. Sodium oxybate is well established for narcolepsy (not approved for OSA). Xywav (lower-sodium oxybate) expanded the label to idiopathic hypersomnia. No substantial change in clinical positioning is anticipated.

**Side-effect profile:** The principal adverse events are nausea, dizziness, headache, and enuresis. Sodium oxybate is a Schedule III controlled substance with a Risk Evaluation and Mitigation Strategy (REMS) due to its sedative properties and potential for abuse, respiratory depression, and CNS depression when combined with alcohol or other sedatives. It must be administered at bedtime in two divided doses and is subject to stringent distribution controls.

**Overall validation:** High for narcolepsy. The only agent with robust evidence for both EDS and cataplexy reduction. Not applicable to OSA.

**Comparison to solriamfetol:** The two compounds address different aspects of narcolepsy management and are frequently used in combination. Solriamfetol provides direct daytime wake promotion, while sodium oxybate provides nocturnal sleep consolidation and cataplexy control. Solriamfetol is approved for both narcolepsy and OSA; sodium oxybate is approved only for narcolepsy (and idiopathic hypersomnia for Xywav). The combination has been used in clinical practice without characterized antagonistic interactions.

## 12.6 Comparator summary

The five comparators span the mechanistic spectrum of clinically available wake-promoting and anti-sleepiness agents. **Modafinil** and **armodafinil** are the established first-line agents with the longest clinical track records, the broadest prescribing experience, and generic availability, but with modestly lower ESS effect sizes than solriamfetol in indirect comparisons and with CYP-mediated drug interaction liabilities. **Pitolisant** represents the most mechanistically novel comparator through its histaminergic mechanism, with the practical advantage of non-scheduled status but a narrower approved indication and a lower ESS effect size. **Methylphenidate** is the historical reference compound with extensive clinical use but limited modern evidence, higher abuse potential, and Schedule II classification. **Sodium oxybate** is mechanistically orthogonal as a nighttime sleep consolidator and cataplexy agent, complementary rather than competing with solriamfetol.

Solriamfetol occupies a distinctive position in this landscape: it is the only approved DNRI, the only agent with demonstrated TAAR1 agonist activity, and the only compound with registration-quality evidence in both narcolepsy and OSA showing ESS effect sizes at the upper end of the class. Its pharmacokinetic profile (high bioavailability, negligible hepatic metabolism, no CYP interactions, renal elimination) is among the most favorable in the comparator panel, with the single limitation of renal-impairment sensitivity. The Schedule IV classification places it at the same regulatory level as modafinil and below methylphenidate and sodium oxybate. The absence of monoamine-releasing activity provides a mechanistic rationale for the lower abuse profile relative to amphetamine-type agents.

Investigators considering solriamfetol for research applications in wakefulness, arousal, or dopaminergic/noradrenergic pharmacology should recognize its positioning as a reuptake inhibitor without releasing activity, its TAAR1 agonist compo-

nent, and its renal elimination pathway as the three defining pharmacological and pharmacokinetic features that distinguish it from the comparator agents.

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