

# Profile of Solriamfetol in the Management of Excessive Daytime Sleepiness Associated with Narcolepsy or Obstructive Sleep Apnea: Focus on Patient Selection and Perspectives

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**Abstract:** Excessive sleepiness (ES) is a symptom of obstructive sleep apnea (OSA) and narcolepsy that has severe consequences. Wake-promoting drugs and stimulants are utilized as accessory treatment in OSA to reduce propensity to sleep but they do not improve sleep-disordered breathing. Solriamfetol is a first-line therapeutic agent to combat sleepiness in OSA and narcolepsy patients that is approved both by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). For excessively sleepy adult patients with OSA despite primary treatment or narcolepsy patients without cataplexy, solriamfetol may be used as initial therapy or as replacement therapy in patients who fail treatment or experience unacceptable side effects with modafinil, armodafinil, pitolisant, or stimulants. It can also be used as add-on therapy in OSA or narcolepsy patients when ES is only partially controlled with modafinil, armodafinil, pitolisant, sodium oxybate, or stimulants. Solriamfetol is a phenylalanine derivative whose wake-promoting action may be mediated through its selective dopamine and norepinephrine reuptake inhibition. This paper reviews the profile of solriamfetol in treating ES associated with OSA or narcolepsy and discusses patient selection and clinical perspectives. Mechanism of action, pharmacology, pharmacokinetics, clinical efficacy, and tolerability of solriamfetol are described. The Treatment of OSA and Narcolepsy Excessive Sleepiness (TONES) solriamfetol trials demonstrated the efficacy of solriamfetol in reducing propensity to sleep and maintaining wakefulness, with significant improvements in mean maintenance of wakefulness test (MWT) sleep latencies and significant reduction in Epworth Sleepiness Scale (ESS) scores compared to placebo. With solriamfetol, significantly higher percentages of patients showed improvement in patient's and clinician's global impression of change.

**Keywords:** excessive daytime sleepiness, obstructive sleep apnea, narcolepsy, solriamfetol, drug profile, clinical perspective

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## Introduction

Excessive sleepiness (ES) refers to difficulty maintaining desired wakefulness and alertness during the day with unintended lapses into drowsiness or sleep. Daily functioning is significantly impaired in excessively sleepy persons with obstructive sleep apnea (OSA) or narcolepsy.<sup>1,2</sup> ES is associated with reduced attention, cognitive dysfunction, impaired performance of psychomotor tasks, decreased work productivity, interference with social and occupational function, reduced

health-related quality of life (QOL), and increased risk of motor vehicular and workplace accidents.<sup>1,3-9</sup>

OSA is characterized by repetitive episodes of partial or complete collapse of the upper airway during sleep associated either with a cortical arousal or oxygen desaturation.<sup>10</sup> It affects 9%-38% of the general population and is associated with increased likelihood of hypertension, cardiovascular disease including coronary artery disease and atrial fibrillation, stroke, diabetes mellitus type 2, motor vehicle accidents, and diminished quality of life.<sup>11-15</sup> Daytime sleepiness occurs with OSA in 14% and 5% of affected men and women, respectively.<sup>11</sup> OSA is heterogeneous, and different phenotypes can determine response to different primary therapies. Nasal continuous positive airway pressure (PAP) therapy is the treatment of choice, but alternatives include nasal expiratory PAP, oro-PAP, orthodontic oral appliances, surgical modification of the upper airway, implantable hypoglossal nerve stimulation, myofunctional therapy of the oropharynx and tongue, and pulmonary rehabilitation.<sup>16-19</sup> With pharmacotherapy, there is no drug currently available with large enough effect size to serve as primary therapy for OSA. Despite primary therapy, residual excessive sleepiness (RES) can persist in 5%-55% percent of patients treated with PAP and other therapies.<sup>20-22</sup>

The US Food and Drug Administration (FDA) has approved wake-promoting agents (WPAs) such as modafinil, armodafinil, and solriamfetol as accessory treatment in OSA, although these do not treat the underlying sleep-disordered breathing.<sup>1</sup> Meanwhile, solriamfetol is the only drug currently approved by the European Medicines Agency (EMA) to treat ES in OSA patients; the agency withdrew its marketing approval of modafinil for ES in OSA in July 2010 due to safety concerns relating to psychiatric disorders, skin reactions, and significant off-label use and potential for abuse.<sup>23,24</sup>

Traditional stimulants (methylphenidate, dexamethylphenidate, amphetamine/dextroamphetamine, methamphetamine, lisdexamfetamine) have been used off-label to treat ES in OSA in both the USA and Europe. Although effective, rebound hypersomnolence is present with amphetamines and methylphenidate.<sup>25</sup> Additionally, amphetamines and methylphenidate have adverse cardiovascular side effects and increased potential for abuse and addiction.<sup>25</sup> For these reasons, traditional stimulants are not first-line agents for the treatment of ES in OSA, but they still seem to be commonly used in the clinical setting.

OSA patients with residual ES may be difficult to treat and may need a trial of different drugs or a combination of medications.<sup>25-29</sup> A survey of physicians reported treatment failures in 28% with a single WPA, 15% with 2 agents, and 8% with 3 or more WPAs.<sup>25,26</sup> Prior studies had shown that 49% of OSA patients with ES fail to respond to modafinil and 45% fail to respond to armodafinil.<sup>28,29</sup> These treatment failures underscore the need for more effective alternative drugs.

In a retrospective analysis of healthcare claims during a 4.75-year period, 12.4 million patients with OSA (mean age 56 years, 40% female) were identified.<sup>26,27</sup> Comorbidities included hypertension (57%), diabetes (31%), cardiovascular disease (CVD, 29%), and major depressive disorder (20%).<sup>26,27</sup> Five percent of OSA patients received  $\geq 1$  stimulant (methylphenidate/amphetamines) or WPA (modafinil/armodafinil). Patients with OSA who received stimulants/WPAs were younger (mean age 47 years), 42% female, with hypertension in 48% and CVD in 19%. Among OSA patients without comorbidities, 6% were prescribed stimulant/WPA versus 3.5% of patients with OSA and CVD.<sup>26,27</sup>

Among patients with OSA and hypertension taking these drugs, 63% received amphetamines or methylphenidate and 46% received modafinil or armodafinil (9% received a combination of these drugs).<sup>26,27</sup> In OSA patients with CVD who received stimulants/WPAs, 57% received amphetamines or methylphenidate and 52% received modafinil or armodafinil (9% received a combination of these drugs). The presence of hypertension and CVD comorbidities did not seem to influence whether a stimulant versus WPA was prescribed.<sup>27</sup>

Narcolepsy is a life-long central nervous system disorder with a symptom pentad consisting of ES (the presenting symptom in ~90% of patients), cataplexy (the most specific symptom), sleep paralysis, hypnagogic hallucinations, and disrupted nocturnal sleep.<sup>30,31</sup> Narcolepsy is categorized into narcolepsy type 1 (NT1) or narcolepsy type 2 (NT2) depending on the presence of cataplexy and/or low cerebrospinal hypocretin levels in the former and their absence in the latter.<sup>31</sup> Type 1 prevalence is estimated at 0.02%-0.18% in the US and Western Europe, while the prevalence of Type 2 is estimated at 20.5/100,000 (0.0205%).<sup>31</sup>

At this time, there is no cure for narcolepsy. Current therapy for narcolepsy is symptom-based, with the goal to allow the fullest return of normal function. Among the WPAs utilized for narcolepsy, modafinil, armodafinil,

solriamfetol, and pitolisant are approved by the FDA, while modafinil, solriamfetol, and pitolisant are approved by the EMA. Stimulants such as methylphenidate, dextromethylphenidate, and amphetamines (amphetamine/dextroamphetamine, methamphetamine, lisdexamfetamine) remain as second-line drugs for ES in narcolepsy, because sympathomimetic side effects, rebound hypersomnia, high abuse potential, and tolerance are problematic.<sup>30</sup> In narcolepsy with cataplexy, WPAs/stimulants are usually add-on drugs, since these agents (except for pitolisant, sodium oxybate, and mazindol) have no effect on other narcolepsy symptoms, such as cataplexy, sleep disruption, hypnagogic or hypnopompic hallucinations, or sleep paralysis. Mazindol is an appetite suppressant and a non-amphetamine central nervous system stimulant that blocks dopamine and norepinephrine reuptake. Although it was withdrawn from the US and European markets in 1999 unrelated to its efficacy or safety, it is still used in many countries.<sup>32–34</sup> Mazindol has been used off label in Europe and Japan to treat narcolepsy symptoms of sleep attacks and cataplexy<sup>32</sup> and has been used in France in patients with drug-resistant narcolepsy and hypersomnia.<sup>33</sup> Mazindol is a second-line drug with numerous contraindications and drug–drug interactions; a few isolated cases of pulmonary arterial hypertension have been reported.<sup>35</sup>

The choice of a drug to treat ES in either narcolepsy or OSA requires understanding the patient's complaint(s), treatment goals, and past experiences with WPAs/stimulants; reviewing co-morbidities, psychiatric history, and use of lifestyle substances/drugs; and choosing a drug that best fits the patient. The purpose of this review is to present the profile of solriamfetol as a treatment option, focusing on patient selection and perspectives.

## Introduction to Solriamfetol

Solriamfetol hydrochloride (Sunosi<sup>TM</sup>), previously known as JZP-110 and ADX-NO5, is approved in the USA as a WPA to improve ES in adults with narcolepsy or OSA and in Europe in adults with narcolepsy or OSA whose ES is not satisfactorily treated by primary OSA therapy.<sup>1,23</sup> It is available as film-coated tablets containing 75 mg or 150 mg of solriamfetol; the 75 mg tablet is functionally scored to yield 37.5 mg dosing. It is administered once daily, upon awakening. For OSA, the starting dose is 37.5 mg. For narcolepsy, the starting dose is usually 75 mg, but if sleepiness is severe, a dose of 150 mg may be considered. The dose may be doubled after at least 3-day intervals to a maximum of 150 mg per day.<sup>1</sup>

## Clinical Pharmacology: Mechanism of Action, Pharmacodynamics, Pharmacokinetics

Solriamfetol is a phenylalanine derivative with the systematic name (R)-2-amino-3-phenylpropylcarbamate hydrochloride.<sup>1</sup> The mechanism of its wake-promoting action is unclear, but its efficacy may be mediated through its activity as a selective dopamine (DA) and norepinephrine (NE) reuptake inhibitor (DNRI).<sup>1,36</sup> It binds to DA and NE transporters with low affinity and inhibits the reuptake of DA and NE with low potency.<sup>1</sup> It has no binding affinity for serotonin transporter and does not inhibit serotonin re-uptake.<sup>1</sup> It has no appreciable binding affinity to gamma amino butyric acid (GABA), adenosine, histamine, orexin, benzodiazepine, muscarinic acetylcholine or nicotinic acetylcholine receptors.<sup>1</sup>

Following oral administration at doses ranging from 42 to 1008 mg, solriamfetol exhibits dose-dependent linear pharmacokinetics with steady state reached in 3 days.<sup>1</sup> Solriamfetol has oral bioavailability of 95% and reaches peak plasma concentration (T<sub>max</sub>) at 2 hours (median, range 1.25–3 hours) post-dose under fasting conditions.<sup>1</sup> It can be taken with or without food. Ingestion with a high-fat meal minimally changes maximum concentration (C<sub>max</sub>) and area under the curve (AUC), although T<sub>max</sub> is delayed by about 1 hour.<sup>1</sup> Solriamfetol has low protein binding capacity and has an elimination half-life (T<sub>1/2</sub>) of 7.1 hours. It is minimally metabolized. Based on in vitro data, the FDA indicates that clinically significant pharmacokinetic drug interactions with major cytochrome P450 (CYP 450) enzymes and transporters are not expected.<sup>1</sup> Most of the clearance is renal. With active tubular secretion, ~95% of the dose is excreted in the urine unchanged and <1% is excreted as a minor metabolite.<sup>1</sup> Pharmacokinetics is not affected by age, gender, or race.<sup>1</sup>

In patients with renal impairment, the half-life of solriamfetol increases 1.2-, 1.9-, and 3.9-fold in patients with mild, moderate, or severe renal impairment, respectively.<sup>1</sup> In general, T<sub>max</sub> values are not affected by renal impairment. Dose adjustments are needed for moderate or severe renal impairment, but not for mild renal impairment.<sup>1</sup> Solriamfetol is not recommended for use in patients with end-stage renal disease (eGFR <15 mL/min/1.73 m<sup>2</sup>) as both exposure (area under the curve) and half-life are significantly increased in these patients.<sup>1</sup> Hemodialysis removes an average of 21% of solriamfetol.<sup>1</sup>

## Clinical Efficacy Trials

The Treatment of OSA and Narcolepsy Excessive Sleepiness (TONES) trials 1–5 established the safety and efficacy of solriamfetol in improving ES associated with narcolepsy or cataplexy.<sup>1,37–42</sup> The TONES 2–5 studies included two 12-week, double-blind efficacy trials—one in participants with narcolepsy (TONES 2)<sup>39</sup> and the other in participants with OSA (TONES 3)<sup>40</sup>—and two withdrawal trials—a 6-week double-blind trial in patients with OSA (TONES 4)<sup>41</sup> and a long-term (52-week) open-label trial in narcolepsy and OSA subjects (TONES 5).<sup>42</sup>

The FDA's approval of solriamfetol was based upon the results of the TONES Phase 3 trials that established robust effects of solriamfetol in improving ES associated with narcolepsy or OSA.<sup>1</sup> Primary endpoints in the TONES trials were maintenance of wakefulness test (MWT) mean sleep latency (SL) and the mean Epworth Sleepiness Scale (ESS) score on solriamfetol compared to placebo.<sup>1</sup> Solriamfetol's efficacy in reducing sleepiness was present after 1 week. Table 1 presents efficacy data for the TONES 2–5 clinical trials.

### TONES 1 (Narcolepsy)

A 4-week, Phase 2 crossover trial<sup>37</sup> and a 12-week, phase 2B parallel group trial (TONES 1)<sup>38</sup> displayed significant improvements in 40-minute MWT SL and ESS scores in solriamfetol-treated narcolepsy participants at doses of 150 mg and 300 mg when compared to placebo.<sup>37,38</sup> Post-hoc analysis of the phase 2B trial results showed that a  $\geq 25\%$  reduction in ESS scores might be useful to identify narcolepsy patients who respond to solriamfetol.<sup>38,43</sup> A secondary endpoint was the percentage of participants who reported improvement on the Patient Global Impression of Change (PGI-C) and/or Clinical Global Impression of Change (CGI-C) on solriamfetol compared to placebo.<sup>1</sup>

### TONES 2 (Narcolepsy)

In TONES 2, narcolepsy participants were randomized to 75 mg, 150 mg, or 300 mg/day solriamfetol or placebo.<sup>39</sup> In this trial, the MWT SL improved significantly in a dose-dependent manner at the 150 mg and 300 mg solriamfetol doses, but not at the 75 mg dose compared to placebo.<sup>39</sup> ESS scores significantly improved in a dose-dependent manner for the 75 mg, 150 mg, and 300 mg/day solriamfetol groups compared to placebo.<sup>39</sup> There was a significant increase in the percentage of patients who

reported improvement in their overall condition at doses of 75 mg, 150 mg, and 300 mg of solriamfetol compared to placebo, and the improvement was dose dependent over the 12 weeks of the study.<sup>39</sup>

Solriamfetol was effective in treating ES in patients with narcolepsy regardless of cataplexy status as shown by robust effects on MWT, ESS, and PGI-C.<sup>44</sup> According to the EMA, post-hoc cumulative distribution analysis of the results from the narcolepsy trial demonstrated that only 15.5% of placebo patients achieved an ESS score  $\leq 10$  compared to almost double at 30.5% in the 75 mg and more than triple at 49.2% in the 300 mg/day solriamfetol groups.<sup>23</sup> In the 150 mg/day group, mean ESS score decreased from 17.0 at baseline to 11.1 at week 12.<sup>23</sup> In narcolepsy patients, solriamfetol at doses of 150 mg and 300 mg also improved measures of functional status, health-related QOL, work productivity, and reduced activity impairment compared to placebo.<sup>45</sup>

### TONES 3 (OSA)

In TONES 3, OSA participants were randomized to receive 37.5 mg, 75 mg, 150 mg, or 300 mg/day solriamfetol or placebo.<sup>40</sup> In this phase 3 trial, the change from baseline in SL on each of the 5 individual MWT trials at week 12 was significantly greater for the solriamfetol 75 mg, 150 mg, and 300 mg groups compared to placebo, but the 37.5 mg group showed a significant difference relative to placebo for trial 2 only.<sup>40</sup> ESS scores significantly improved in all solriamfetol treatment groups (37.5 mg, 75 mg, 150 mg and 300 mg) compared to placebo.<sup>40</sup> PGI-C percentages showed significant improvement for the 75 mg, 150 mg, and 300 mg treatment groups compared to placebo, but not the 37.5 mg group.<sup>40</sup>

Post-hoc cumulative distribution analysis of results from this OSA trial showed that more than 70% of patients in the solriamfetol 150 mg and 300 mg groups achieved ESS score  $\leq 10$ , compared to 37.7% of placebo patients.<sup>23</sup>

Solriamfetol improved measures of functional QOL and work productivity in OSA participants with ES compared to placebo.<sup>46,47</sup> Patients were randomized to receive solriamfetol 37.5 mg, 75 mg, 150 mg and 300 mg, or placebo. At baseline, about 49% of participants were employed, and presenteeism (working despite illness, etc., often resulting in reduced productivity) ranged from 43.5% to 47% across treatment groups.<sup>46,47</sup> Absenteeism was relatively low at baseline, with patients missing 2.6% to 5% of work per week. Activity impairment outside of work ranged from



**Table 1** Efficacy of Solriamfetol for Treatment of Excessive Sleepiness in Narcolepsy and OSA in Clinical Trials

Trial, Condition	Treatment Groups (Number Analyzed for Efficacy)	Design, Duration, Endpoints	ESS Score	MWT (Sleep Latency)	Patient Global Impression of Change (%)	Clinical Global Impression of Change (%)
Phase 2b, Narcolepsy TONES 2 <sup>38</sup>	Solriamfetol 150 mg/day x 4 weeks then 300 mg/day x 8 weeks (n=44) Placebo (n=49)	Phase 2b, randomized, double-blind, placebo-controlled trial 12 weeks. Primary: Δ MWT SL, Δ CGI-C baseline to week 12; Secondary: Δ ESS, PGIC baseline to week 12	ESS mean baseline scores 17.3 to 17.4 across groups. Mean change from baseline: Solriamfetol -8.5, Placebo -2.5, p<0.0001	MWT mean baseline values 5.7 across groups. Mean (SE) change from baseline: Solriamfetol 12.8 (1.6), Placebo 2.1 (1.2), p<0.0001	PGI-C mean baseline values %, 83.7 to 53.2 across groups. Mean change from baseline: Solriamfetol 93.0, Placebo 38.3, p<0.0001	CGI-C mean baseline values %, 83.7 to 55.3 across groups. Mean change from baseline: Solriamfetol 86.0, Placebo 38.3, p<0.0001
Phase 3, Narcolepsy TONES 2 <sup>39</sup>	Solriamfetol 75 mg/day (n=59) Solriamfetol 150 mg/day (n=55) Solriamfetol 300 mg/day (n=59) Placebo (n=58)	Phase 3, randomized, double-blind, placebo-controlled trial 12 weeks. Primary: Δ MWT SL, Δ ESS baseline to week 12; Secondary: Δ PGIC-C baseline to week 12	ESS mean baseline scores 16.9 to 17.3 across groups. Mean change from baseline, LS mean (SE): Solriamfetol 75 mg -3.8 (0.7), p<0.05. Solriamfetol 150 mg -5.4 (0.7), p<0.0001. Solriamfetol 300 mg -6.4 (0.7), p<0.0001. Placebo -1.6 (0.7) Difference from placebo, LS mean (95% CI): Solriamfetol 75 mg -2.2 (-4.0 to -0.3), p=0.0211; Solriamfetol 150 mg -3.8 (-5.6 to -2.0), p<0.0001; Solriamfetol 300 mg -4.7 (-6.6 to -2.9), p<0.0001	MWT mean baseline values 6.1 to 8.7 across groups. Mean change from baseline, LS mean (SE): Solriamfetol 75 mg 4.7 (1.3), p=0.1595. Solriamfetol 150 mg 9.8 (1.3), p<0.0001. Solriamfetol 300 mg 12.3 (1.4), p<0.0001. Placebo 2.1 (1.3) Difference from placebo, LS mean (95% CI): Solriamfetol 75 mg 2.6 (-1.0 to 6.3), p=0.1595; Solriamfetol 150 mg 7.7 (4.0 to 11.3), p<0.0001; Solriamfetol 300 mg 10.1 (6.4 to 13.9), p<0.0001	PGI-C mean baseline values 53.4 to 84.7 across groups. Mean change from baseline, LS mean: Solriamfetol 75 mg 67.8, p<0.05; Solriamfetol 150 mg 78.2, p<0.0001; Solriamfetol 300 mg 84.7, p<0.0001. Difference from placebo LS mean (95% CI): Solriamfetol 75 mg 28.1 (10.8 to 45.5), p=0.0023; Solriamfetol 150 mg 38.5 (21.9 to 55.2), p<0.0001; Solriamfetol 300 mg 45.1 (29. to 60.7), p<0.0001	CGI-C mean baseline values 50 to 88.1 across groups. Mean change from baseline, LS mean: Solriamfetol 75 mg 69.5, p<0.05; Solriamfetol 150 mg 83.6, p<0.0001; Solriamfetol 300 mg 83.1, p<0.0001
Phase 3, OSA TONES 2 <sup>3,40</sup>	Solriamfetol 37.5 mg/day (n=56) Solriamfetol 75 mg/day (n=58) Solriamfetol 150 mg/day (n=116) Solriamfetol 300 mg/day (n=115) Placebo (n=114)	Phase 3, randomized, double-blind, placebo-controlled trial 12 weeks. Primary: Δ MWT SL, Δ ESS baseline to week 12; Secondary: Δ PGI-C baseline to week 12	Mean ESS baseline scores 14.8 to 15.6 across groups. Mean change from baseline to week 12, LS mean (SE): Solriamfetol 37.5 mg -5.1 (0.64), Solriamfetol 75 mg -5.0 (0.62), Solriamfetol 150 mg -7.7 (0.44), Solriamfetol 300 mg -7.9 (0.46), Placebo -3.3 (0.45). LS mean difference (95% CI): Solriamfetol 37.5 mg -1.9 (-3.4 to 0.3), p=0.0161; Solriamfetol 75 mg -1.7 (-3.2 to -0.2), p=0.0233; Solriamfetol 150 mg -4.5 (-5.7 to -3.2), p<0.0001; Solriamfetol 300 mg -4.7 (-5.9 to -3.4), p<0.0001	MWT mean baseline values 12.0 to 13.6 across groups. Mean change from baseline to week 12, LS mean (SE): Solriamfetol 37.5 mg 4.74 (1.4), Solriamfetol 75 mg 9.08 (1.4), Solriamfetol 150 mg 10.96 (1.0), Solriamfetol 300 mg 12.99 (1.0), Placebo 0.21 (1.0). Difference from placebo, LS mean (95% CI): Solriamfetol 37.5 mg 4.5 (1.2 to 7.90), p=0.0086; Solriamfetol 75 mg 8.9 (5.6 to 12.1), p<0.0001; Solriamfetol 150 mg 10.7 (8.1 to 13.4), p<0.0001; Solriamfetol 300 mg 12.8 (10.0 to 15.6), p<0.0001	PGI-C mean baseline values 47.4 to 82.5% across groups. % Improved at week 12: Solriamfetol 37.5 mg 55.4, Solriamfetol 75 mg 72.4, Solriamfetol 150 mg 89.7, Solriamfetol 300 mg 88.7, Placebo 49.1. % Difference from Placebo: (95% CI) Solriamfetol 37.5 mg 6.2 (-9.7 to 22.2), p=0.4447; Solriamfetol 75 mg 23.3 (8.6 to 38.0), p=0.0035; Solriamfetol 150 mg 40.5 (29.8 to 51.3), p<0.0001; Solriamfetol 300 mg 39.6 (28.7 to 50.4), p<0.0001	CGI-C mean baseline values 46.5 to 82.6% across groups. Difference from placebo (NS): Solriamfetol 37.5 mg 58.9, Solriamfetol 75 mg 70.7, p<0.05; Solriamfetol 150 mg 90.5, p<0.0001; Solriamfetol 300 mg 88.7, p<0.0001

(Continued)

**Table 1 (Continued).**

Trial, Condition	Treatment Groups (Number Analyzed for Efficacy)	Design, Duration, Endpoints	ESS Score	MWT (Sleep Latency)	Patient Global Impression of Change (%)	Clinical Global Impression of Change (%)
Phase 3, OSA TONES 4 <sup>1</sup>	All solriamfetol doses (75 mg/day, 150 mg/day, or 300 mg/day) (n=60) Placebo (n=62) during withdrawal phase	Phase 3 randomized withdrawal (RW) study: 2 weeks of clinical titration, then 2 weeks of stable dose, then 2 weeks randomization to solriamfetol or placebo. Primary: Δ ESS and Δ MWT SL week 4 to 6; Secondary: Δ PGI-C and CGI-C	RW study ESS mean baseline scores 15.3 to 16.0 across groups. ESS score week 4 was 5.9 to 6.4 across groups. During RW, difference from baseline, LS mean (SE), Solriamfetol -0.1 (0.7), Placebo 4.5 (0.7) Difference from placebo, LS mean (95% CI): -4.6 (-6.4 to -2.8), p <0.0001	MWT mean SL baseline 12.3 to 13.1 across groups. MWT mean SL week 4 was 29.0 to 31.7 across groups. During RW LS mean (SE) change, Solriamfetol -1.0 (1.4), Placebo -12.1 (1.3) Difference from placebo, LS mean (95% CI): 11.2 (7.8 to 14.6), p<0.0001	Mean PGI-C % worse at week 6: Solriamfetol 20%, Placebo 50% Mean difference % worsening Solriamfetol compared to Placebo (95% CI): -30 (-46.0 to -14.0), p <0.001	Mean CGI-C % worse at week 6: Solriamfetol 21.7%, Placebo 59.0% Mean difference % worsening Solriamfetol compared to Placebo (95% CI): -37.3 (-53.50 to -21.19), p <0.0001
Long-term study, Narcolepsy or OSA TONES 5 <sup>42</sup>	All solriamfetol doses (75 mg/day, 150 mg/day, or 300 mg/day) Maintenance phase (n=643) Withdrawal phase Solriamfetol (n=140) Placebo (n=142)	2 weeks of titration followed by maintenance phase (up to 50 weeks). After 6 months, subgroups were randomized to solriamfetol or placebo and underwent 2-week withdrawal phase. Primary: Δ ESS; Secondary: Δ PGI-C and Δ CGI-C	Mean baseline ESS scores were 15.9 and 16.2 for groups A and B. During maintenance, mean ESS scores were 7.6 and 7.8. During withdrawal phase, LS mean change from baseline was 1.6 for solriamfetol and 5.3 for placebo. LS mean difference (95% CI) from placebo: -3.7 (-4.80 to -2.65), p<0.0001	Not applicable	During maintenance phase, 87.1 to 90.4% group A and 86.8 to 96.4% group B improved. During withdrawal phase, worsening with solriamfetol 28.2%, Placebo 64.5%, p<0.0001	During maintenance phase, 88.2 to 91.6% group A and 89.5 to 97.6% group B improved. During withdrawal phase, worsening with solriamfetol 28.7%, Placebo 63.8%, p<0.0001

**Notes:** Epworth Sleepiness Score (ESS): Assesses propensity to sleep in 8 everyday situations (0 = would never doze to 3=high chance of dozing), with maximum total ESS score of 24; scores > 10 are considered abnormally sleepy. Changes in ESS scores from baseline to study endpoint are reflected in this table. Maintenance of wakefulness test (MWT) 40 minutes mean sleep latency (SL): Quantifies the ability to remain alert under soporific circumstances for a given period of time. The endpoint measures a change in mean SL time (in minutes) as determined from the first 4 trials of a 40-minute MWT from baseline to week 12 (for TONES 2 and 3). Clinical Global Impression of Severity: A 7-point scale with 1= being normal or not at all ill to 7=most extremely ill. Assessments evaluating changes in status are made by either the patient (PGI-C) or the clinician (CGI-C). The endpoint is the percentage of subjects reported as improved (minimally, much, or very much) at week 12 or in the randomized withdrawal trials (TONES 4 and 5) or as the percentage of subjects reported as worse.

**Abbreviations:** NS, not significant; RW, randomized withdrawal; SE, standard error; Δ, change.

37.8% to 44.3%.<sup>46</sup> At week 12, improved functioning and reduced impairment were observed with solriamfetol 150 mg and 300 mg doses on the basis of improvements in Functional Outcomes of Sleep Questionnaire (FOSQ) total score, overall work impairment, activity impairment, and physical component summary.<sup>46,47</sup> The mental component summary improved only with the 150 mg dose. Presenteeism improved with both 150 mg and 300 mg of solriamfetol. At the lower doses (37.5 mg and 75 mg), there were no significant differences from placebo for the above parameters.<sup>46,47</sup> There were no consistent changes in percentage of work time missed (absenteeism) with solriamfetol relative to placebo.<sup>46,47</sup>

## TONES 4 and TONES 5 Withdrawal Trials (OSA and Narcolepsy)

TONES 4 and 5 were withdrawal trials (See Table 1) wherein patients experiencing a clinical response with a stable dose of solriamfetol were randomized to continue with the drug or switched to placebo.<sup>41,42</sup> In both TONES 4 and 5, the group that was switched to placebo had a statistically significant worsening in ESS scores compared to those who remained on solriamfetol.<sup>41,42</sup> In the overall population of participants in TONES 5, baseline ESS values were 15.9 and 16.2 for group A (study duration 40 weeks) and group B (study duration 52 weeks), respectively.<sup>42</sup> During the titration and maintenance phases with solriamfetol, ESS improved to normal values (mean ESS for group A was 7.6 and 7.8 for group B).<sup>42</sup> Post-hoc analysis of TONES 5 showed that 43% of participants with narcolepsy and 84.5% of OSA participants reported ESS<10, compared to 0.5% and 0.6% of participants with narcolepsy or OSA in the parent study.<sup>42</sup> At the final assessment prior to withdrawal, 87.1%-90.4% of participants in group A and 86.8%-96.4% of participants in group B reported improvement. At 150 mg/day, the highest dose that is approved by EMA and FDA for narcolepsy, patients may still perceive mild sleepiness (mean ESS 11.1).<sup>42</sup> In OSA patients, at 150 mg/day (the highest dose approved by the FDA), about 70% of patients will not be sleepy (ESS score  $\leq 10$ ).<sup>42</sup> Beneficial effects appear to extend long term. Sustained improvements were also reported on Clinical Global Index of Change (CGI-C).<sup>42</sup> During the withdrawal phase, a significantly greater percentage of participants in the placebo group reported worsening compared with the solriamfetol group on both the PGI-C and CGI-C.<sup>42</sup> No rebound hypersomnia occurred

during the withdrawal phase.<sup>42</sup> There was no pattern of withdrawal signs or symptoms after abrupt discontinuation of solriamfetol. Although sleepiness improved, the use of solriamfetol was not associated with a decrease in primary OSA therapy over the course of the 12-week study or in the 52-week extension study.<sup>40,42</sup>

## TONES 1-4 Meta-Analysis

A recent meta-analysis of the safety and efficacy of solriamfetol in treating ES associated with narcolepsy or OSA pooled the outcome measures from 5 trials (TONES 1-4).<sup>37-41,48</sup> Results of the meta-analysis indicated the overall mean difference for MWT was 9.93 min (95% CI: 8.25 to 11.61) and the mean difference of ESS score was -4.44 (95% CI: -5.50 to -3.38), both favoring solriamfetol over placebo.<sup>48</sup> A dose-related effect was shown in this meta-analysis: mean difference in MWT at 75 mg was 5.79 (95% CI: -0.39 to 11.96),  $p=0.066$ ; at 150 mg was 9.48 (95% CI: 6.48 to 12.49),  $p<0.001$ ; and at 300 mg was 11.80 (95% CI: 9.33 to 14.28),  $p<0.001$ .<sup>48</sup> These results indicate that the mean difference in MWT was significant at the 150 and 300 mg doses, but not at the 75 mg dose.

The mean difference in ESS at 75 mg was -1.89 (95% CI: -3.08 to -0.7),  $p=0.002$ ; at 150 mg it was -4.23 (95% CI: -5.27 to -3.19),  $p<0.001$ ; and at 300 mg it was -4.66 (95% CI: -5.71 to -3.60),  $p<0.001$ .<sup>48</sup> These results show that at these various doses of solriamfetol (75 mg, 150 mg, 300 mg), ESS scores were significantly reduced. The difference in mean ESS scores was much greater between the 75 and 150 mg doses than between the 150 and 300 mg doses; the lesser difference between the 150 and 300 mg doses might represent a ceiling effect of these therapeutic doses.

In this meta-analysis, a subgroup analysis compared the narcolepsy patients to the OSA patients, and there was no statistical difference in the mean MWT latencies between the 2 groups.<sup>48</sup> An overall significant improvement of PGI-C and CGI-C by 40.2% and 36.5% was also reported.<sup>48</sup>

This meta-analysis excluded data from the long-term trial<sup>42</sup> to avoid duplication of results.<sup>48</sup> In doing so, it did not capture the long-term benefits in reducing ES to a normal level (ESS <10) in the post-hoc analysis, as previously discussed, nor did it reflect the differences in the long-term responses between the narcolepsy and OSA patients.<sup>42,48</sup>

## Conclusion

The TONES studies showed short-term and long-term efficacy of solriamfetol in promoting wakefulness and

reducing propensity to sleep as well as in improving quality of life and work performance in OSA and narcolepsy patients. At the highest dose approved by the FDA and EMA (150 mg), solriamfetol improved functional outcomes including activities and work impairment.

## Safety and Tolerability

Solriamfetol appears to be mostly well tolerated. TONES 2, 3, and 4 had similar safety and tolerability results. In the OSA trial (TONES 3), the adverse reactions that resulted in discontinuation in more than one solriamfetol-treated patient and at a higher rate than placebo were anxiety (<1%), palpitations (<1%), and restlessness (<1%).<sup>40</sup> During the long-term study (TONES 5), 9.2% had adverse events (AEs) that led to withdrawal.<sup>42</sup> These included anxiety (1.1%), headache (0.6%), insomnia (0.6%), irritability (0.6%), nausea (0.6%), depression (0.3%), and dry mouth (0.3%).<sup>42</sup>

The incidence of AEs was higher with solriamfetol compared to placebo (TONES 2, 68.4% vs 45.8%; TONES 3, 67.9% vs 47.9%; TONES 4 Titration Phase, 48.9% vs 10.2%).<sup>1,39–41</sup> In the 12-week studies in narcolepsy and OSA, serious AEs (SAEs) were reported in 1.05% of the solriamfetol-treated patients compared to 0.88% in the placebo group.<sup>1</sup> There were slightly more SAEs in the narcolepsy patients (3/220) compared to the OSA patients (3/353).<sup>1</sup> SAEs in the solriamfetol groups included anxiety, bile duct obstruction, acute cholecystitis, conversion disorder, hyperglycemia, non-cardiac chest pain, and streptococcal endocarditis.<sup>1</sup>

In the TONES 5 trial, cardiovascular SAEs were reported in 9/643 subjects receiving 150 mg to 300 mg of solriamfetol compared to none in the placebo group.<sup>42</sup> All these cardiovascular SAEs occurred in OSA participants (n=417) and included myocardial infarction, cerebrovascular accident, atrial fibrillation, angina pectoris, and coronary artery disease.<sup>42</sup> Of these SAEs, two were deemed by the investigators to be related to study drug administration—atrial fibrillation in a participant on concomitant thyroid medications and cerebrovascular accident in a participant with hypertension.<sup>42</sup> Serious cardiovascular adverse events were not reported in the narcolepsy participants.

A meta-analysis of data from 5 solriamfetol trials reported that the overall risk ratio of adverse events with solriamfetol was 1.47 (95% CI: 1.28 to 1.69) compared to placebo.<sup>48</sup> One or more AE was reported by 64.1% of patients in the solriamfetol group compared to 39.1% in

the placebo group.<sup>48</sup> The most common AEs ( $\geq 5\%$ ) from solriamfetol reported both in the FDA review and in the meta-analysis were headache, nausea, reduced appetite, anxiety, and insomnia.<sup>1,48</sup> Headache was transient, and most of these side effects occurred within the first two weeks.<sup>1</sup> Insomnia was present in 9.5% of solriamfetol treated participants compared to 1.7% in placebo and was mild or moderate in severity.<sup>40</sup> No statistically significant or clinically meaningful changes were noted in polysomnography parameters of total sleep time, number of awakenings, or wake after sleep onset.<sup>40</sup> Psychiatric side effects included jittery feeling, anxiety, irritability, bruxism, and restlessness.<sup>1,25,38,40</sup>

Solriamfetol produced modest increases in blood pressure (BP) and pulse rate. After 12 weeks of therapy, mean systolic BP increases from baseline were 3.1 and 6.8 mm Hg in narcoleptic participants versus 3.8 and 4.5 mm Hg in OSA participants for the 75 mg and 300 mg groups, respectively.<sup>1</sup> Twenty-four-hour BP monitoring in narcolepsy patients on solriamfetol compared to those on placebo did not demonstrate an increase in the percentage of non-dippers (defined as <10% decrease in mean arterial pressure during sleep) in the solriamfetol group compared to the placebo group.<sup>49</sup> Mean heart rate (HR) increases were slightly greater in narcolepsy (3.7 and 6.5 beats/min) compared to OSA (3.3 and 4.5 beats/min) at doses of 75 mg and 300 mg, respectively.<sup>1</sup> The increases in BP and HR were observed early in the morning (~6–8 AM) and tapered in the evening (~4–8 PM).<sup>23,49</sup> There was a dose-dependent rise in incidence of increased HR, increased BP, and palpitations.<sup>23</sup> HR increases resolved after a mean duration of 3–20 days and no case was rated as severe. Observed cases of increased BP lasted between 20 and 96 days across dose arms. Palpitations had a mean duration of 2.5–10.5 days and no cases were rated as severe.<sup>23</sup> In a randomized, double-blind, four-period, placebo- and positive-controlled crossover study, the effects of solriamfetol 300 mg and 900 mg on QTc interval were studied and demonstrated minimal risk of QTc prolongation.<sup>50</sup> The FDA's review of this study concluded that a dose of 300 mg of solriamfetol (which is twice the highest FDA-approved dose) did not prolong the corrected QT interval by Fredericia (QTcF) to a clinically relevant extent.<sup>1</sup>

There were no deaths with solriamfetol use in the 12-week trials (TONES 2 and 3). A 70-year-old OSA participant in TONES 5 who had multiple medical co-morbidities and was on immunosuppressive agents developed



a myocardial infarction associated with sepsis and died.<sup>1,42</sup> The investigators believed the death was unrelated to study drug administration.<sup>42</sup>

## Pregnancy and Lactation

There are no adequate data on the use of solriamfetol in pregnant women. A pregnancy exposure registry has been established, but there are no published results. Available data from case reports are insufficient to determine drug-associated risks of miscarriage, major birth defects, or adverse maternal or fetal outcomes.<sup>1</sup> There are no data available on the presence of solriamfetol or its metabolites in human milk, the effects on milk production, or the effects on the breast-fed infant. Breast-fed infants should be monitored for agitation, anorexia, insomnia, and reduced weight gain.<sup>1</sup>

## Pediatric and Geriatric Use

Safety and efficacy in pediatric patients with narcolepsy or OSA have not been established, and clinical studies in pediatric patients have not been conducted.<sup>1</sup> Thirteen percent of patients in the narcolepsy and OSA trials were 65 years and over. There were no clinically meaningful differences in safety or effectiveness between elderly and adult patients. For elderly patients with mild renal failure, dosage adjustment is not needed, but dose adjustments are recommended in patients with moderate to severe renal impairment.<sup>1</sup>

## Drug Abuse, Dependence, and Overdosage

Solriamfetol is a Schedule IV drug. It has the potential for abuse. A study showed that solriamfetol produced Drug Liking scores similar to or lower than phentermine.<sup>1</sup> When considering placing a patient on solriamfetol, physicians should evaluate for a recent history of drug abuse, particularly in those with a history of stimulant (methylphenidate, amphetamine, cocaine) or alcohol abuse, follow them closely, and monitor for signs of misuse or abuse of solriamfetol, such as drug-seeking behavior or escalating doses.<sup>1</sup> Abrupt discontinuation of solriamfetol after use of at least 6 months did not produce a pattern of adverse events in participants that was suggestive of physical dependence or withdrawal.<sup>1</sup> There is no specific reversal agent for solriamfetol overdose. Hemodialysis removes approximately 21% of the drug. Overdoses should be

managed with primarily supportive care including cardiovascular monitoring.<sup>1</sup>

## A Clinical Approach to Patient Selection and Perspectives

### What Approach Should Be Utilized in Choosing a WPA/Stimulant for ES in OSA or Narcolepsy? OSA

The approach to treating patients with OSA and excessive sleepiness starts with personalizing therapy for the patient. Focus on the patient's needs and concerns and address any underlying sleep deprivation, co-morbidities, other sleep disorders, mood disorders, and drugs/substances that contribute to ES. What activities cannot be performed due to ES? What is the impact of ES on quality of life and safety? What improvements are being sought? Determine the disease phenotype and match with psychosocial factors.<sup>51</sup> The different OSA phenotypes include the elderly, female, non-anatomic factors (low arousal threshold or sensitive chemo reflex), REM-related, supine predominant, complete concentric palatal collapse, and excessive daytime sleepiness. Correlate the phenotype with risk factors and natural history, clinical features, pathophysiology, biologic markers, outcomes, genomics, and genetics.<sup>51</sup> Individualize treatment protocols. Optimize primary treatment of OSA to increase adherence. With PAP therapy, address mask fit problems and use desensitization if needed, improve humidification, and address any difficulties with prescribed pressures or devices. Reinforce commitment to therapy by encouraging patients to view the patient screen daily, providing them with desired parameters on apnea hypopnea index and leak percentage, and instructing them when to contact their provider for assistance. Analyze available data from technologic devices, track the patient's progress, and give timely feedback.

Obtain baseline subjective and objective measures of ES and QOL and monitor regularly to assess efficacy of prescribed treatments. Subjective measures can include ESS, FOSQ, Fatigue Severity Scale (FSS), Patient Health Questionnaire (PHQ-9), or Patient-Reported Outcomes Measurement Information System (PROMIS-7). Objective measures may include multiple sleep latency test (MSLT), MWT, and the Psychomotor Vigilance Task (PVT). Customize and utilize a patient-centered approach to selecting a wake-promoting agent. Explore and

understand the patient's main therapeutic goal(s) as they may differ from the clinician's priority set. Common goals in the treatment of ES in OSA include mitigation of cardiovascular or metabolic risk, reduction of daytime sleepiness, increased ability to participate in activities of daily living, including driving, and improved quality of life.<sup>52</sup> The other determinants in prescribing a specific drug, such as solriamfetol, to treat ES include drug–drug interactions, side effects, efficacy, co-morbidities and lifestyle choices, and insurance/direct cost to the patient.

### Narcolepsy

Treatment of narcolepsy patients is symptomatically based and consists of drugs and behavioral therapies, including regular bedtimes, allowing enough time in bed at night, and taking scheduled naps during the day. Use of lifestyle substances (caffeine, alcohol, nicotine, and cannabis) also need to be reviewed and discussed. Pharmacotherapy should be customized based upon the patient's age, characteristics, and symptoms, with the most incapacitating symptom(s) targeted first. The choice of a drug may also be affected by drug availability in the country where it is prescribed. In the absence of cataplexy, ES can be treated with monotherapy with a WPA such as solriamfetol, pitolisant, modafinil, or armodafinil. Secondary therapies for ES include stimulants such as methylphenidate, amphetamines, and mazindol. In the presence of ES and cataplexy, primary treatment modalities would be sodium oxybate or pitolisant as these drugs address both symptoms. In a study of central hypersomnias (including narcolepsy types 1 and 2 and idiopathic hypersomnia), 39% of patients had a complete response to treatment, 25% had a partial response, and 36% had a poor response to therapy.<sup>53</sup> For patients with residual symptoms after first-line treatment, combination therapy improved daytime sleepiness in 55% of these patients.<sup>53</sup> Combination therapy, such as with sodium oxybate and modafinil, may result in synergistic effects to further improve ES.<sup>54</sup> When there are several first-line agents to choose from, the choice of a drug requires balancing drug efficacy, convenience of administration, development of drug tolerance, managing drug effects, considering comorbidities, monitoring for evidence of drug abuse, and choosing drugs partly based on insurance carrier's "allowed" drugs and patient's co-pay.<sup>30</sup> It is important to regularly assess the effects after treatment is started in order to adjust dosages or timing of dosages, to discontinue or switch to a different medication, or to decide on combination therapy.

### Who are Candidates for Treatment with Solriamfetol?

For residual ES in adult patients with OSA despite primary treatment or in narcolepsy patients without cataplexy, solriamfetol may be used as (1) initial or replacement therapy in patients who have failed treatment or experienced unacceptable side effects with either modafinil, armodafinil, pitolisant, or stimulants, or as (2) add-on therapy in OSA and narcolepsy patients with or without cataplexy when ES is only partially controlled with either modafinil, armodafinil, pitolisant, sodium oxybate, or stimulants.

### Who are Not Candidates for Treatment with Solriamfetol?

Patients who are being treated concurrently with a monoamine oxidase inhibitor (MAOI) or who have used an MAOI within the preceding 14 days should not receive solriamfetol.<sup>1</sup> Patients with myocardial infarction within the past year, unstable angina pectoris, uncontrolled hypertension, serious cardiac arrhythmias, and other serious heart problems should not receive solriamfetol.<sup>23</sup> In addition, patients with end-stage renal disease (eGFR <15 mL/min/1.73 m<sup>2</sup>) are not candidates for treatment with solriamfetol.<sup>1</sup>

### What Advantages, if Any, Does Solriamfetol Hold Over Other Therapies?

Solriamfetol is efficacious and has an acceptable side effect profile. For patients with ES due to OSA or narcolepsy who have comorbid liver disease or who are taking medications that are metabolized through the cytochrome P450 (CYP450) enzymes, including hormonal contraceptives, solriamfetol may be a good option. Unlike modafinil, armodafinil, and pitolisant, which are metabolized primarily by the liver, solriamfetol is not a substrate for any of the major drug metabolizing CYP enzymes and does not induce CYP1A2, 2B6, 3A4, or UDP-glucuronosyl transferase 1A1 (UGT1A1) enzymes.<sup>23,30</sup> This is an important consideration in women of childbearing age because modafinil, armodafinil, and pitolisant can reduce the efficacy of hormonal contraceptive therapy.<sup>23,30</sup> If any of these other agents is utilized, supplemental non-hormonal birth control measures should be employed in addition to hormonal contraceptive therapy. The reduced efficacy of hormonal therapy can last up to 21 days after discontinuation of modafinil, armodafinil, or pitolisant.<sup>23</sup>

Another potential advantage of solriamfetol over modafinil or armodafinil is its long duration of action. In

narcolepsy subjects, sustained effects were present through the 5th trial of MWT at 7–9 hours post-dose, while modafinil or armodafinil effects were waning by the 5th trial of MWT.<sup>55</sup> This longer duration of action of solriamfetol may be useful in OSA or narcolepsy patients who complain that ES is worse in the mid or late afternoon when they take either modafinil or armodafinil and who are not interested in split-dosing or an extra dose of medication.

## How Does Solriamfetol Compare with Other Agents in Terms of Efficacy in Controlling ES?

### OSA

There are no studies that provide direct comparison of efficacy of solriamfetol to other WPAs in OSA or narcolepsy. For OSA patients, indirect comparison of results from TONES 3 on changes in mean MWT SL and ESS scores compared to results from a meta-analysis of OSA patients using modafinil or armodafinil suggests that solriamfetol may have a bigger impact on improving wakefulness and reducing sleepiness than modafinil or armodafinil.<sup>25,40,56</sup> In this meta-analysis, MWT SL significantly improved with modafinil and armodafinil with weighted mean difference (WMD) in MWT SL of 2.51 minutes for modafinil and 2.71 minutes for armodafinil.<sup>56</sup> By comparison, MWT least squares (LS) mean difference significantly improved by 8.9, 10.7 and 12.8 minutes with solriamfetol at doses of 75 mg, 150 mg, and 300 mg, respectively.<sup>40</sup> ESS also significantly improved, with WMD  $-2.96$  for modafinil and WMD of  $-2.63$  for armodafinil.<sup>56</sup> Similarly, ESS LS mean difference improved by  $-1.7$ ,  $-4.5$ , and  $-4.7$  for solriamfetol doses of 75 mg, 150 mg, and 300 mg, respectively.<sup>56</sup> A caveat regarding this indirect comparison is that 150 mg/day is the highest approved dosage for solriamfetol. Additionally, the above meta-analysis used the MWT 20 minutes,<sup>56</sup> while TONES used the MWT 40 minutes.<sup>40</sup>

### Narcolepsy

There are no direct studies comparing solriamfetol to other WPAs or stimulants in treating ES in narcolepsy patients. Indirect comparison may be made with pitolisant. In HARMONY 1, ESS LS mean difference from baseline for pitolisant compared to placebo was  $-3.1$ , while in HARMONY 1bis, mean difference was  $-2.2$ .<sup>57,58</sup> For comparison, TONES 2 showed ESS LS mean difference from baseline for solriamfetol was  $-4.7$  at 300 mg,  $-3.8$  at

150 mg, and  $-2.2$  at 75 mg compared to placebo.<sup>39</sup> For MWT results, HARMONY 1 showed MWT LS mean difference of 1.47 and HARMONY CTP showed MWT LS mean difference of 1.78 compared to placebo.<sup>57,58</sup> In TONES 2, MWT LS mean differences compared to placebo were 10.14 at 300 mg, 7.65 at 150 mg, and 2.26 at 75 mg of solriamfetol.<sup>39</sup> These indirect comparison results suggest that solriamfetol may be more efficacious in reducing sleepiness and improving wakefulness compared to pitolisant, particularly at higher doses of 150 mg and 300 mg.

A study in narcolepsy subjects utilizing MWT censored to 20 minutes reported that the mean SL change from baseline for solriamfetol was 8.9 minutes, whereas mean changes from baseline reported in other publications for modafinil 400 mg were 2.0 and 2.3 minutes, armodafinil 250 mg was 2.6 minutes, dextroamphetamine 60 mg was 5.8 minutes, and methylphenidate 60 mg was 3.6 minutes.<sup>55</sup> These findings suggest that in narcolepsy patients, solriamfetol 300 mg is more efficacious in promoting wakefulness than modafinil 400 mg, armodafinil 250 mg, methylphenidate 60 mg, or dextroamphetamine 60 mg.<sup>55</sup> In their meta-analysis of solriamfetol, Subedi et al performed indirect comparisons of ESS and MWT results from trials of various drugs: they concluded that compared to other wake-promoting drugs, such as pitolisant, modafinil, armodafinil, and sodium oxybate, solriamfetol resulted in more significant improvement in both MWT and ESS score and appeared to be more efficacious.<sup>48</sup> Caveats in the comparisons between solriamfetol and other drugs listed above include the fact that the highest approved dosage for OSA or narcolepsy patients is 150 mg daily, improvements in ESS and MWT SL are dose-related, and the study populations for the different studies may have different attributes.

## Does Solriamfetol Affect Driving Performance?

Patients with narcolepsy and OSA are at increased risk for driving accidents with increased vehicular crash rates and near misses.<sup>59,60</sup> Driving performance in narcolepsy subjects ( $n=24$ ) and in OSA subjects ( $n=34$ ) on solriamfetol was assessed in a randomized, double-blind, placebo-controlled study in which driving performance during an on-road driving test was assessed at 2 hours and 6 hours post-dose following 7 days of treatment with solriamfetol (150 mg/day x 3, then 300 mg/day x 4) or placebo.<sup>61,62</sup>

Baseline mean ESS score for the OSA group was 14.4 but was not stated for narcolepsy.<sup>61,62</sup> The standard deviation of lateral position (SDLP), a measure of “weaving,” was assessed. In narcolepsy subjects, SDLP for solriamfetol was significantly lower than placebo at 2 hours, but was not statistically significant at 6 hours.<sup>61</sup> In OSA subjects, SDLP measurements at 2 hours and at 6 hours were significantly lower with solriamfetol compared with placebo.<sup>62</sup> These results suggest that driving performance may be improved by solriamfetol in narcolepsy patients or sleepy OSA patients.

## Is There a Difference in Response Based on Age, Gender, or Ethnicity?

In the pooled summary of 12-week studies with solriamfetol, there were no differences in the response by age or gender.<sup>1</sup> Most of the participants were white (77.7%), followed by blacks (16.6%), and there were no differences identified by race. There were only 3.5% Asians in the treatment group, and less than 1% of subjects belonged to American Indian or Native Hawaiian or other Pacific Islander groups, and so race differences in these groups of patients is less certain.

## How Does the Side-Effect Profile of Solriamfetol Compare with Other WPA or Stimulants?

Solriamfetol has good tolerability and side effect profile with low discontinuation rate as previously described.<sup>1,38,39</sup> Adverse events  $\geq 5\%$  for solriamfetol-treated groups were headache, anorexia, nausea, constipation, dry mouth, palpitations, insomnia, and anxiety/nervousness/irritability.<sup>1</sup>

With modafinil, AEs  $\geq 5\%$  included headache, nausea, nervousness, rhinitis, back pain, diarrhea.<sup>63</sup> For armodafinil, AEs  $\geq 5\%$  included headache, nausea, dizziness, and insomnia.<sup>64</sup> Serious AEs for modafinil and armodafinil included (1) rare cases of serious or life-threatening rash, including Stevens–Johnson and toxic epidermal necrosis; (2) drug reaction with eosinophilia and systemic symptoms (DRESS) or multi-organ hypersensitivity; (3) angioedema and hypersensitivity; (4) persistent sleepiness without return to normal; (5) psychiatric symptoms, including anxiety, agitation, nervousness, and irritability; (6) potential effects on the ability to drive and use machinery; and (7) cardiovascular events.<sup>63,64</sup> Neither modafinil nor armodafinil should be used in patients with history of left ventricular hypertrophy or in patients who have

experienced mitral valve prolapse syndrome. With armodafinil, small average increases in mean systolic and diastolic blood pressure of 1.2 to 4.3 mm Hg compared to placebo were present, and there was a small average increase in pulse rate from 0.9 to 3.5 beats per minute.<sup>63,64</sup>

For pitolisant, AEs  $\geq 5\%$  included headache, insomnia, nausea, upper respiratory tract infection, arthralgia, and anxiety.<sup>57,58</sup> The most frequent SAEs with pitolisant were psychiatric in nature (depression, psychosis); these occurred in patients who had prior psychiatric histories, and no clear temporal relationship was found between pitolisant use and psychiatric worsening.<sup>58</sup> Pitolisant has significant drug–drug interactions and caution/monitoring should be applied; the EMA and FDA recommendations for dosage adjustments should be considered.<sup>57</sup> Co-administration of pitolisant with a CYP2D6 inhibitor (eg paroxetine, fluoxetine, bupropion) increases the exposure to pitolisant. Strong CYP3A4 inhibitors (eg ketoconazole, itraconazole) have not been shown to increase pitolisant exposure.<sup>57</sup> CYP3A4 inducers (eg rifampin, carbamazepine, phenytoin) reduce pitolisant levels by 50%.<sup>57</sup> H1 receptor antagonists that cross the blood-brain barrier (eg diphenhydramine, promethazine, imipramine, clomipramine) may reduce the effectiveness of pitolisant.<sup>57</sup> Pitolisant and its metabolites may induce CYP3A4 and CYP2B6 at therapeutic concentrations and, by extrapolation, CYP2C, UGTs, and P-gp, but there are no clinical data on the extent of these interactions.<sup>57</sup> There is reduced effectiveness of sensitive C3A4 substrates, such as cyclosporine, midazolam, and hormonal contraceptives.<sup>57</sup> There is mild to moderate QT prolongation (10–13 ms) when pitolisant is administered at 3–6 times the maximum approved dose (108–216 mg), while no significant changes have been noted at therapeutic doses.<sup>57</sup> Patients with cardiac disease, those receiving other QT-prolonging drugs, or those known to be at risk of repolarization disorders require careful monitoring.<sup>57</sup>

For sodium oxybate, common AEs included nausea, dizziness, somnolence, tremor, and enuresis.<sup>65</sup> Significant AEs with sodium oxybate included CNS depression, abuse and misuse, respiratory depression or sleep-disordered breathing, depression and suicidality, other behavioral or psychiatric adverse reactions, parasomnia, and sensitivity to high sodium load.<sup>65</sup>

With methylphenidate, AEs  $\geq 5\%$  included headache, insomnia, upper abdominal pain, decreased appetite, and anorexia.<sup>66</sup> SAEs included sudden death, stroke, and myocardial infarction, and there is also potential for drug



abuse. Methylphenidate should not be used in adults with structural cardiac abnormalities, cardiomyopathy, serious cardiac rhythm abnormalities, coronary artery disease, or other serious cardiac problems. Methylphenidate may increase average blood pressure by 2–4 mm Hg and heart rate by 3–6 bpm.<sup>66</sup> Psychiatric side effects include exacerbation or emergence of new psychotic or manic symptoms, depression, bipolar disorder, and aggression.

The benefit to risk ratio for amphetamines is not well documented.<sup>67</sup> The most common side-effects  $\geq 5\%$  in adults are anorexia, insomnia, dry mouth, diarrhea, nausea, and anxiety.<sup>68</sup> Amphetamines have been associated with sudden death, stroke, and myocardial infarction.<sup>68</sup> They are contraindicated in patients with advanced arteriosclerosis, known structural cardiac abnormalities, cardiomyopathy, serious cardiac arrhythmia, coronary artery disease, moderate to severe hypertension, hyperthyroidism, history of drug abuse, or during or within 14 days of administration of MAO inhibitors.<sup>67</sup> Psychiatric adverse reactions include psychosis or manic symptoms. Peripheral vasculopathy including Raynaud's phenomenon may occur.<sup>68</sup> Co-administration with serotonergic agents may increase the risk of serotonin reaction. Amphetamines have a black box warning of high potential for abuse and dependence.<sup>68</sup>

Mazindol is contraindicated in patients with a history of coronary artery disease, congestive heart failure, cardiovascular disease including arrhythmias, cerebrovascular disease, inadequately controlled or unstable hypertension, pulmonary artery hypertension, anorexia nervosa or bulimia nervosa, psychiatric disorders (depression, schizophrenia, agitation), narrow angle glaucoma, severe renal and hepatic insufficiency, history of drug abuse or dependence, and alcoholism.<sup>34,35</sup> Concomitant use with MAO inhibitors, antipsychotics, or antidepressants is contraindicated. A black box warning is given with regards to association with primary pulmonary hypertension and cardiac valve dysfunction when used for more than 3 months.<sup>34,35</sup>

## Does Solriamfetol Affect Weight Loss, Blood Pressure, or Lipid Abnormalities?

Increased obesity has been reported in patients with narcolepsy and those with OSA. In the 52-week (TONES 5) open-label extension trial in narcolepsy and OSA,  $\sim 26\%$  of subjects reported  $\geq 5\%$  weight loss, while  $\sim 9\%$  reported weight gain. Percentage of patients with weight loss  $\geq 5\%$  increased as solriamfetol doses increased.<sup>69</sup> Among

subjects who lost weight, systolic BP (mean, SD) decreased by  $2.6 \pm 11.4$  and diastolic BP decreased by  $1.0 \pm 9.0$  mm Hg; the percentage of participants with high glucose and triglycerides decreased.<sup>69</sup> Among participants without weight loss, systolic BP increased by  $0.65 \pm 12.5$  mm Hg and diastolic BP increased by  $1.2 \pm 8.7$  mm Hg; the percentage of participants with high glucose increased, but there was no change in percentage with high triglycerides.<sup>69</sup>

## What Caveats Should Be Utilized When Solriamfetol is Prescribed?

### Cardiovascular Effects on BP, HR, and QT Interval

In general, the safety and tolerability profile of solriamfetol, including cardiovascular effects, is acceptable. Solriamfetol use was associated with increases in BP and HR, and during the 52-week study (TONES 5), 9 patients experienced significant cardiovascular events compared to no patients in the placebo group.<sup>42</sup> Because patients with any acute uncontrolled medical condition were excluded from trials, the risk of long-term cardiovascular events in patients with comorbid conditions is unclear.

Because epidemiological evidence shows that even a 2–3 mm Hg increase in existing high BP increases rates of stroke, heart attack, and death,<sup>23</sup> patients with pre-existing hypertension should have their blood pressure controlled before starting solriamfetol. BP and HR should be monitored before therapy is started and periodically during therapy. Potential pharmacodynamic interactions may occur when used with drugs that increase BP and/or HR, and caution should be exercised.

In a small ( $n=18$ ) retrospective study of patients taking stimulants (drugs were not specified), the addition of solriamfetol (75 mg, 150 mg) did not lead to significant increase in systolic or diastolic blood pressure, mean arterial pressure, or heart rate.<sup>70</sup> Because of the small number of participants and retrospective nature of this study, it would be prudent to monitor BP and HR in patients where combination therapy of solriamfetol with a stimulant is prescribed.

### Psychiatric Symptoms

Psychiatric adverse effects including anorexia, anxiety/nervousness, insomnia, and irritability were observed in clinical trials. Patients with acute or untreated psychiatric conditions were excluded from clinical trials, and the effectiveness or safety in these populations is unclear. Solriamfetol should be used with caution in these patient populations.

Caution should also be exercised when solriamfetol is used in patients with a history of psychosis or bipolar disorders. Consider either dose reduction or discontinuation of solriamfetol if psychiatric symptoms develop.

### Angle-Closure Glaucoma

Because of increased norepinephrine signaling with solriamfetol, there may be the potential to induce mydriasis and precipitate angle-closure glaucoma. In all the studies with narcolepsy and OSA, no AEs of acute angle-closure glaucoma were observed in any solriamfetol-treated subjects. However, there were 2 AEs of mydriasis, and therefore caution is advised in patients with increased ocular pressure or risk of angle-closure glaucoma.<sup>23</sup>

### Dose Adjustments for Impaired Renal Function

For patients with mild renal impairment, no dosing changes are needed. For moderate renal impairment, initially dose at 75 mg once daily; if needed, based on efficacy and tolerability, increase at intervals of 7 days to a maximum of 150 mg once daily. For severe renal impairment, initially dose at 37.5 mg once daily; if needed, increase at intervals of 7 days to a maximum of 75 mg per day. Solriamfetol is not recommended in patients with end-stage renal disease.<sup>1</sup>

### Are There Any Disadvantages to Using Solriamfetol Over Other Wake-Promoting Agents/Stimulants?

For patients who are candidates for solriamfetol therapy, the main disadvantage in the US to prescribing this drug is the need in most cases to secure insurance authorization both initially and for refills, resulting in higher costs to the patient if the authorization is denied or often even when it is approved, delay in starting therapy, and greater time expenditure for the prescribing provider.<sup>71–74</sup> Before approving solriamfetol, some formularies require a prior trial and failure of central nervous system stimulants (amphetamines/methylphenidate) and of modafinil or armodafinil, or having contraindications to these agents, and additionally in the case of OSA patients, compliance with PAP therapy.<sup>72,73</sup> Even for drugs that are approved by insurance, there are different tiers of drugs, with the patient's share of cost and deductibles rising with higher tiers.<sup>71</sup> These insurance-related and reimbursement issues may also affect the patient's willingness to try solriamfetol either as initial therapy or add-on therapy.

## Conclusions

Solriamfetol is first-line therapy for residual ES in OSA or narcolepsy, either as initial or replacement or add-on therapy. The TONES 2–5 trials have demonstrated short-term and long-term efficacy in decreasing propensity to sleep, promoting wakefulness, and improving quality of life. Solriamfetol has a good safety profile and acceptable side effects. Compared to the other WPAs, it may be a better choice in patients with comorbid liver disease or in those who are taking medications that are metabolized through the cytochrome P450 enzymes, including hormonal contraceptives. Insurance considerations may also influence whether solriamfetol is prescribed as initial or replacement therapy or add-on therapy in OSA or narcolepsy. As research in both OSA and narcolepsy progresses, more specific therapies may be developed that will affect the role solriamfetol will play in the treatment of these patients.

## Key Points

- Excessive sleepiness has deleterious consequences in patients with OSA and narcolepsy. Despite primary treatment modalities in OSA, residual sleepiness may persist and may be difficult to treat.
- Wake-promoting drugs serve as adjunctive therapy for OSA. Solriamfetol, modafinil, and armodafinil are the only FDA-approved drugs for ES with OSA, and in Europe, only solriamfetol is approved for this indication. Approximately half of OSA patients treated with modafinil or armodafinil fail to improve. Although stimulants such as methylphenidate and amphetamines are used off-label in the clinical setting, these have cardiovascular side effects and have high risk for abuse.
- Treatment in narcolepsy is symptom-based. In patients with narcolepsy with cataplexy, wake-promoting drugs/stimulants are add-on medications, as these agents (except for pitolisant, sodium oxybate, and mazindol) have no effect on other symptoms such as cataplexy, sleep fragmentation, or REM phenomena. For EDS with narcolepsy, wake-promoting drugs such as modafinil, armodafinil, solriamfetol, and pitolisant are approved by the FDA, while modafinil, solriamfetol, and pitolisant are approved by EMA. Stimulants such as methylphenidate and amphetamines are second-line drugs due to sympathomimetic cardiovascular side effects and high risk for abuse. Mazindol is another second-line drug that is available

only in certain countries, has numerous contraindications, and carries a black box warning about primary pulmonary hypertension and cardiac valve dysfunction.

- Solriamfetol is a dopamine-norepinephrine reuptake inhibitor that promotes wakefulness.
- Short- and long-term efficacy of solriamfetol has been demonstrated in TONES trials with dose-dependent reduction in ESS, prolongation in mean SL on MWT, and increased percentages reporting improvement on PGI-C when compared to placebo.
- Solriamfetol is in general well tolerated, and effects were seen within the first week and remained sustained during the 12-week trials. Long-term efficacy was shown by TONES 5 (52-week trial).
- Solriamfetol-associated side effects  $\geq 5\%$  were headache, anorexia, nausea, dry mouth, constipation, palpitations, anxiety/nervousness/irritability, and insomnia. Slight increases in systolic and diastolic blood pressure readings were noted, but no significant cardiovascular effects were reported. No rebound hypersomnolence was present.
- Solriamfetol remains as adjunctive therapy for OSA, but it appears to be an effective drug as initial or replacement therapy for residual ES in OSA patients.
- Solriamfetol appears to be an effective drug for ES in narcolepsy. In patients with narcolepsy with cataplexy, it may be used as add-on therapy when ES is not controlled with medications like sodium oxybate or pitolisant.

## Data Sharing Statement

Not applicable.

## Ethics Approval and Informed Consent

Not applicable (Review).

## Consent for Publication

Yes.

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